# *Introduction*

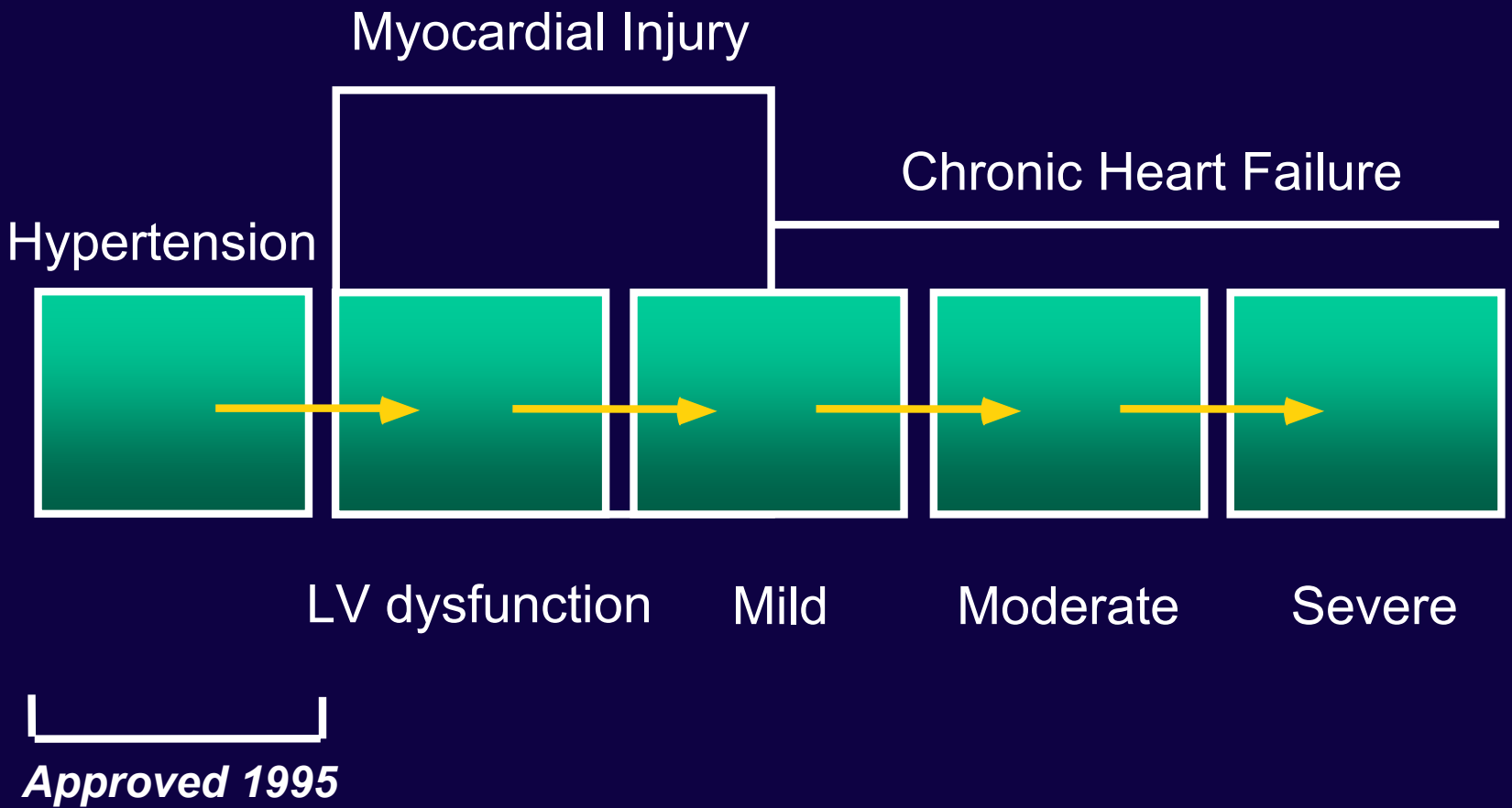
Clare Kahn, Ph.D.

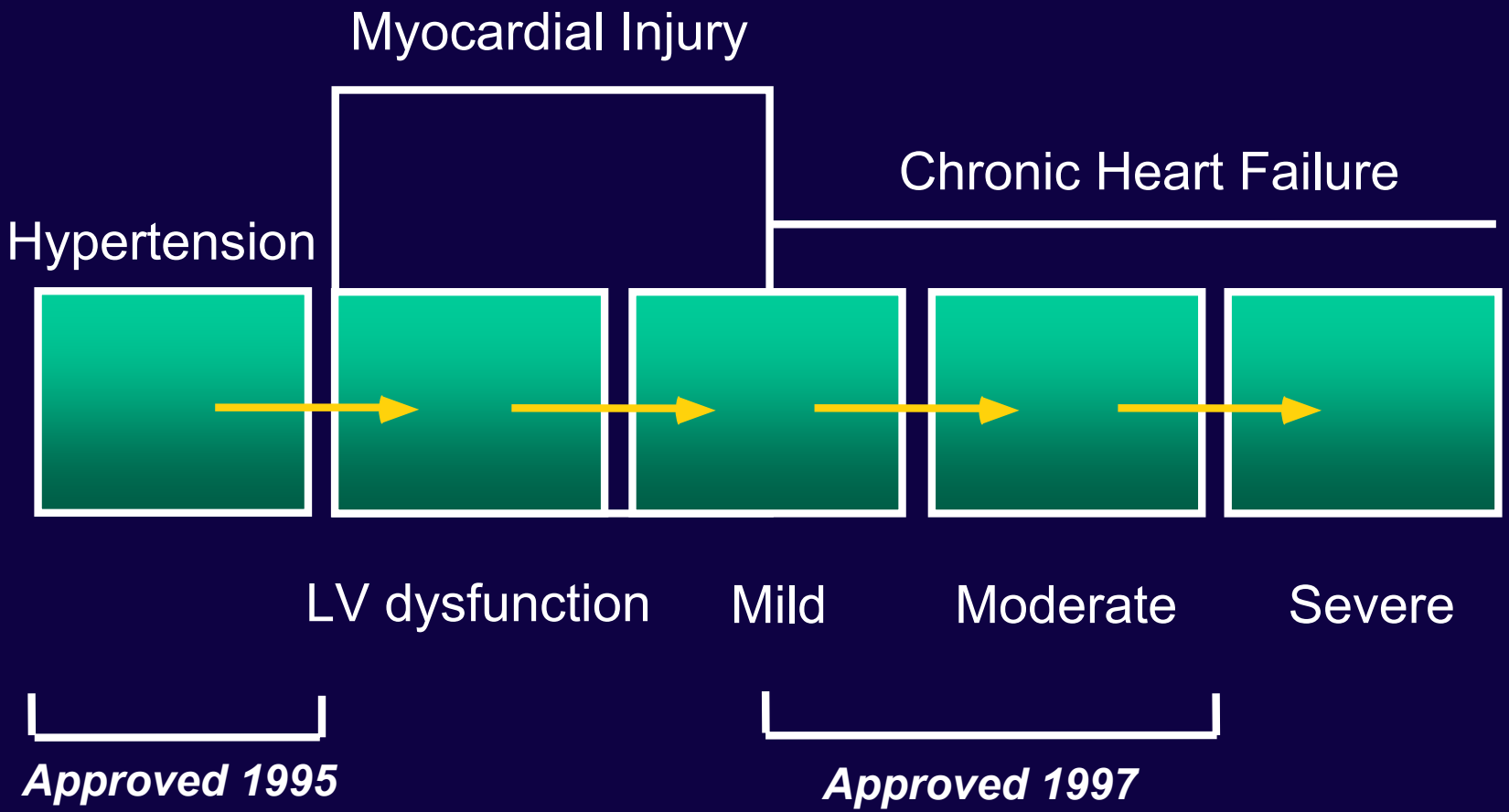
Vice President, US Regulatory Affairs
Cardiovascular, Urogenital & Metabolic Products,
GlaxoSmithKline

# *Carvedilol*

Pharmacological Properties

- Nonselective β-adrenergic receptor antagonist
- $\alpha_1$-adrenergic receptor antagonist


Myocardial Injury
Chronic Heart Failure
Hypertension
LV dysfunction
Mild
Moderate
Severe
Approved 1995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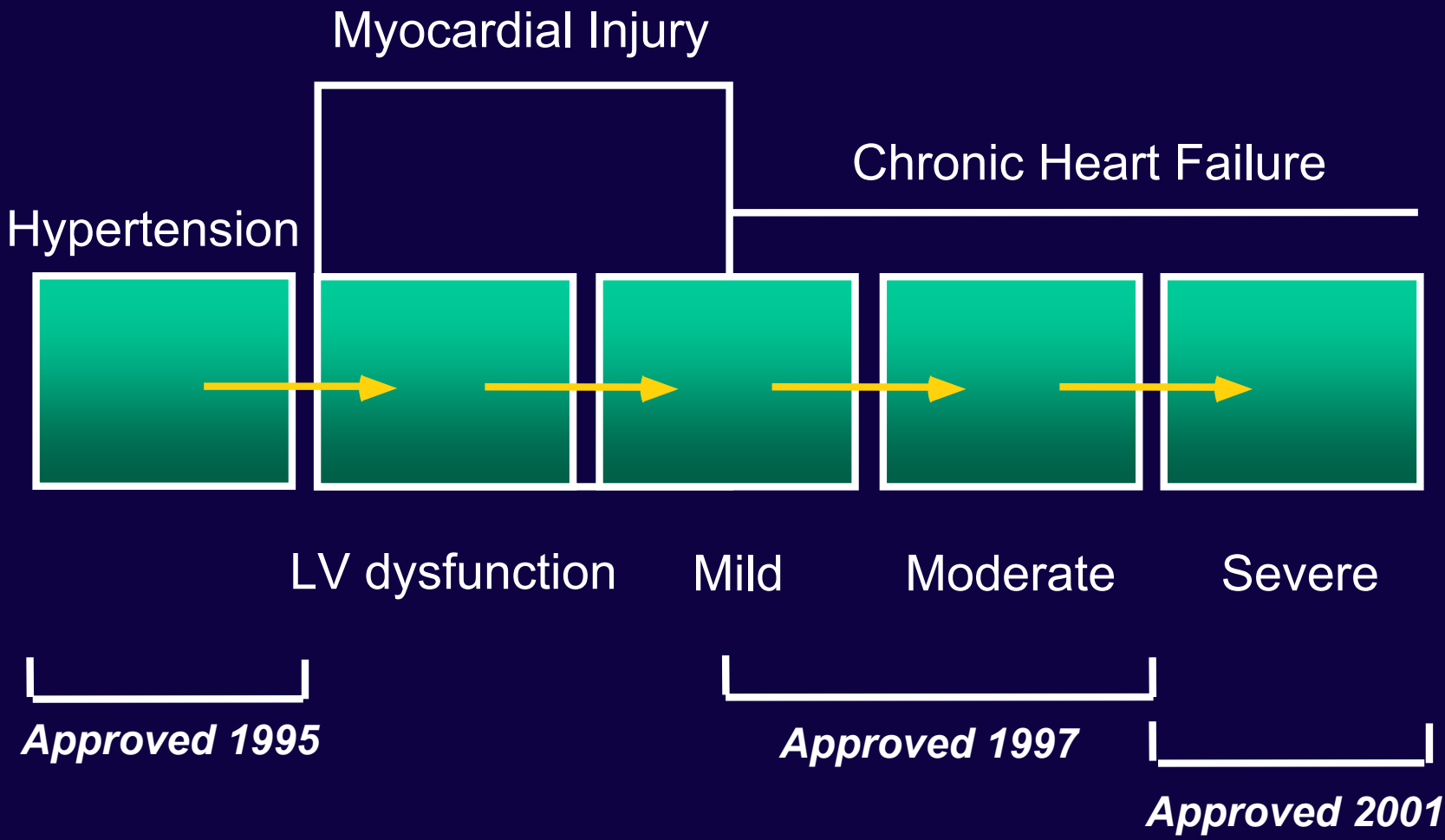
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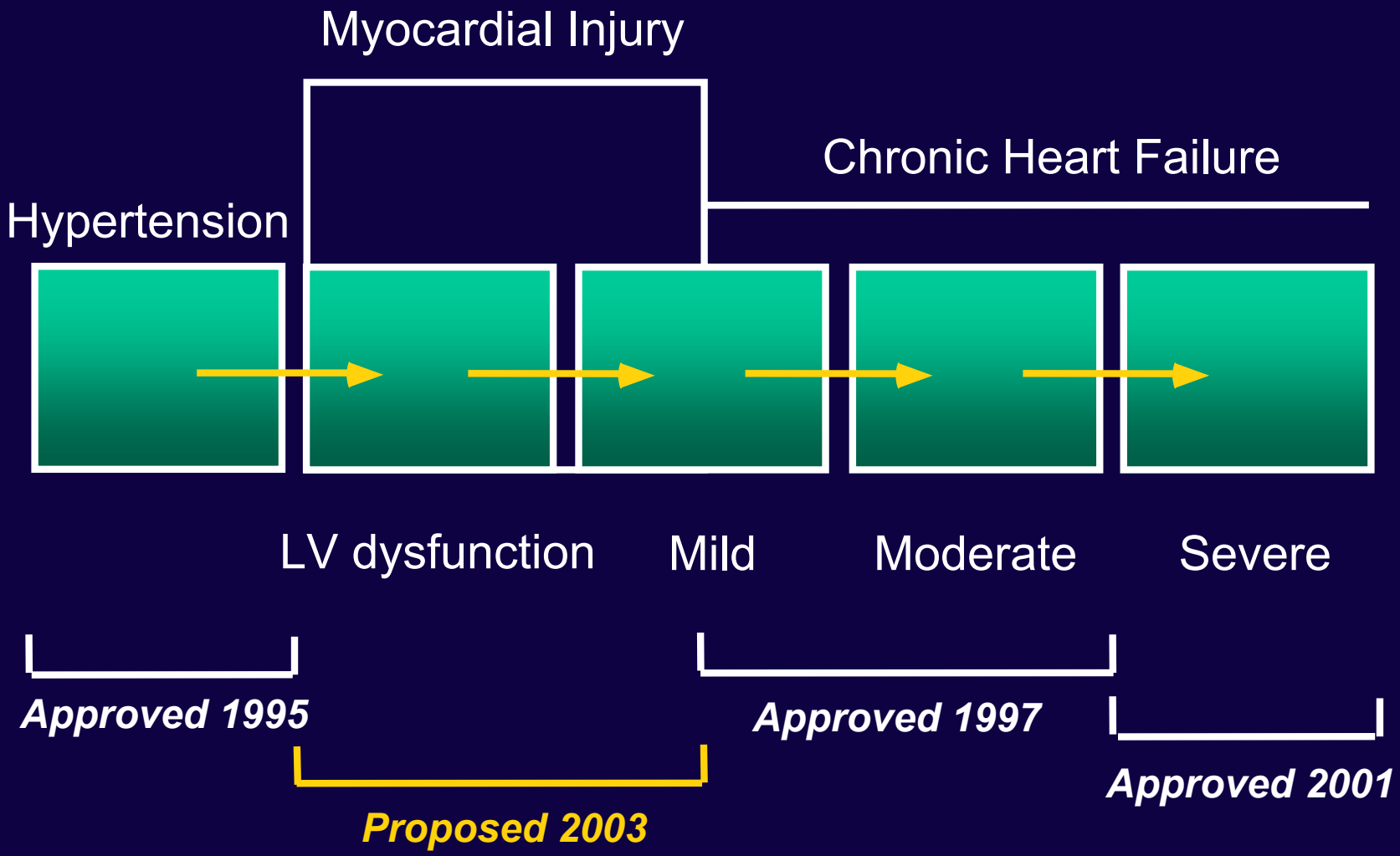
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Proposed 2003

# *Scope of Presentation*

**Use of Beta-blockers in Post-infarction Patients**

**Carvedilol Pilot: "CHAPS"**

**Carvedilol Pivotal Trial**

**"CAPRICORN"**

**Primary Endpoint: All cause mortality**

**DSMB**

**Co-Primary Endpoints:**
**- Death or CV Hospitalization**
**- All cause mortality**

**Labeling**

# *Proposed Indication*

*Coreg* is indicated to reduce mortality and the risk of infarction in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of ≤ 40%.

# *Agenda*

| | |
|---|---|
| Introduction | Clare Kahn, Ph.D. |
| Background to the CAPRICORN Trial | Mary Ann Lukas, M.D. |
| CAPRICORN Trial | |
| Primary Endpoints | Henry Dargie, MB., ChB. |
| Why Are We Here? | Milton Packer, M.D. |
| CAPRICORN Trial Effect on Non-Fatal Events | Henry Dargie, MB., ChB. |
| Safety and Concluding Remarks | Milton Packer, M.D. |

# *Consultants*

**Henry Dargie, MB., ChB.**
University of Glasgow
Principal Investigator, CAPRICORN

**Ian Ford, Ph.D.**
University of Glasgow
Biostatistician, CAPRICORN

**Milton Packer, M.D.**
Columbia University
Planning Committee, CAPRICORN
Principal Investigator, COPERNICUS

**Jonathan Sackner-Bernstein, M.D.**
Columbia University
Endpoint Committee, CAPRICORN

# *Background to the CAPRICORN Trial*

Mary Ann Lukas, M.D.

# *Beta-Blockers Approved for Use in Survivors of An Acute Myocardial Infarction*

- Timolol
- Propranolol
- Metoprolol tartrate (immediate-release)

# *Trials of Beta-Blockers Approved for Use in Survivors of An Acute Myocardial Infarction*

- Norwegian Timolol Trial (timolol)
- Beta-Blocker Heart Attack Trial (propranolol)
- Göteborg Metoprolol Trial (metoprolol)
- Lopressor Intervention Trial (metoprolol)

# *Patient Populations Not Included in Earlier Post-Infarction Trials of β-Blockers*

- High risk patients (e.g., heart failure or systolic BP < 100-110 mm Hg) were generally not enrolled.
- Many currently available treatments for the *immediate* management of the post-infarction patient were not available or used (e.g., ACE inhibitors, IV nitroglycerin, heparin, thrombolytics).
- Many currently available treatments for the *long-term* management of the post-infarction patient were not allowed (e.g., ACE inhibitors, aspirin, anticoagulants or lipid lowering drugs).

# *Should β-blockers Still Be Used in the Post-Infarction Patients in the Modern Era?*

Are β-blockers still needed?

- Trials carried out before advent of ACE inhibitors, thrombolytics, heparin, aspirin, anticoagulants or lipid lowering drugs.

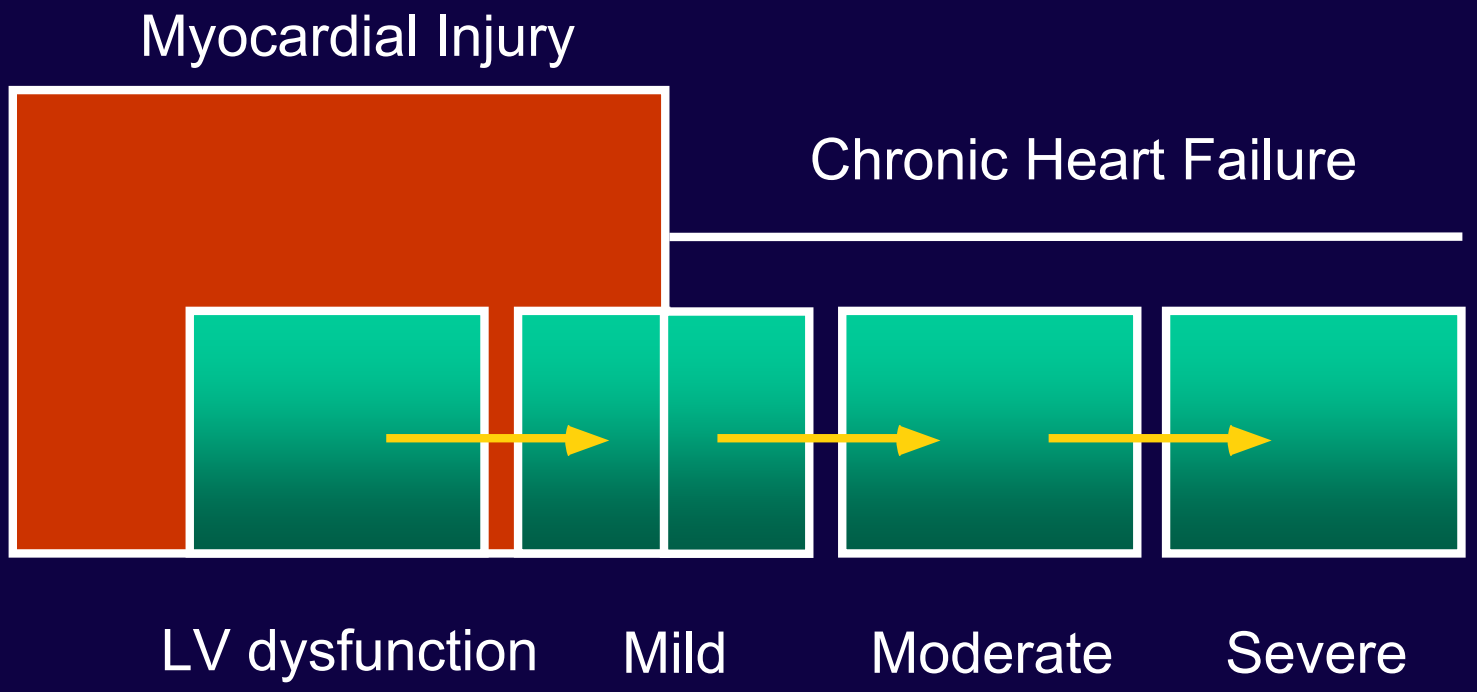
Are β-blockers worth the risks?

- Concerns about risk of worsening heart failure (in patients with low EF) or hypotension (in patients with receiving ACE inhibitors or vasodilators).

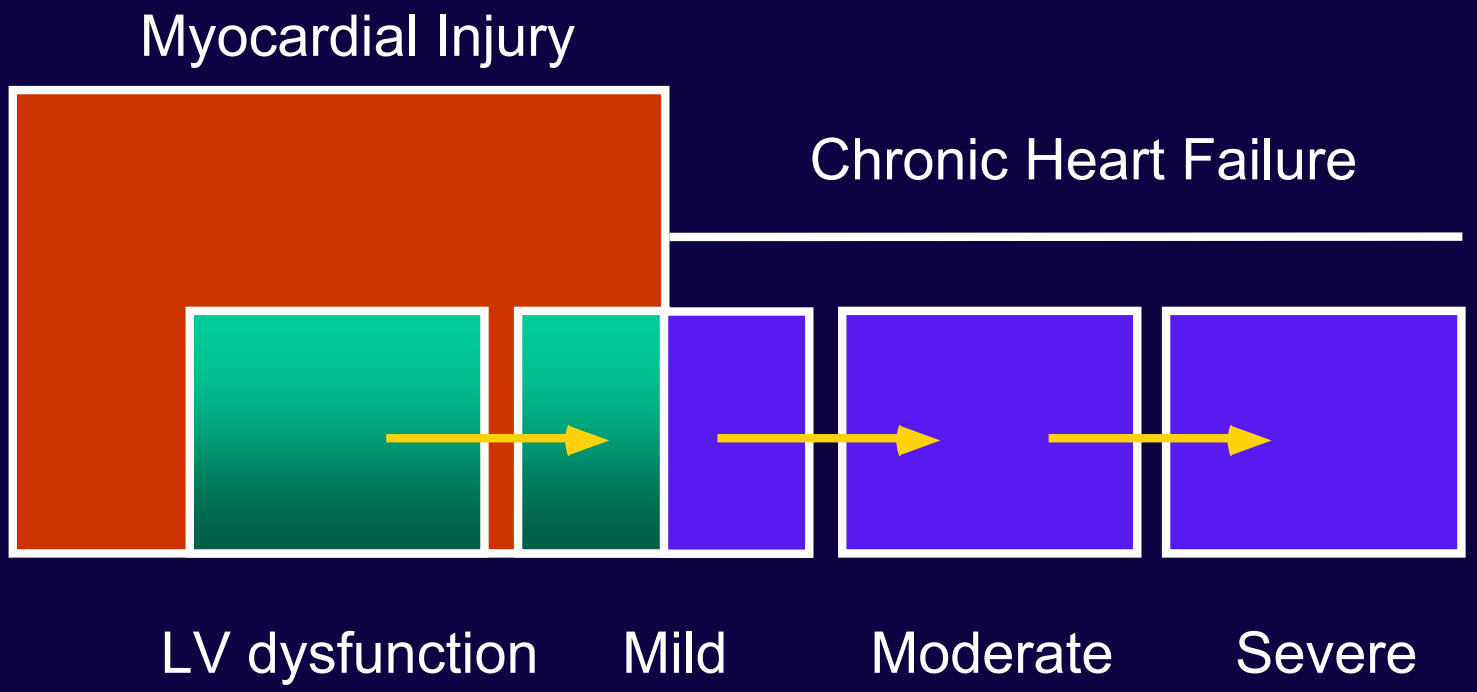
# *To Complicate Matters Further . . .*

- The β-blockers approved for use in post-infarction patients are not approved for heart failure and currently carry a contraindication to their use in heart failure.
  - Timolol, propranolol and immediate-release metoprolol
- The β-blockers approved for use in chronic heart failure are not approved for use following a recent myocardial infarction.
  - Carvedilol and sustained-release metoprolol

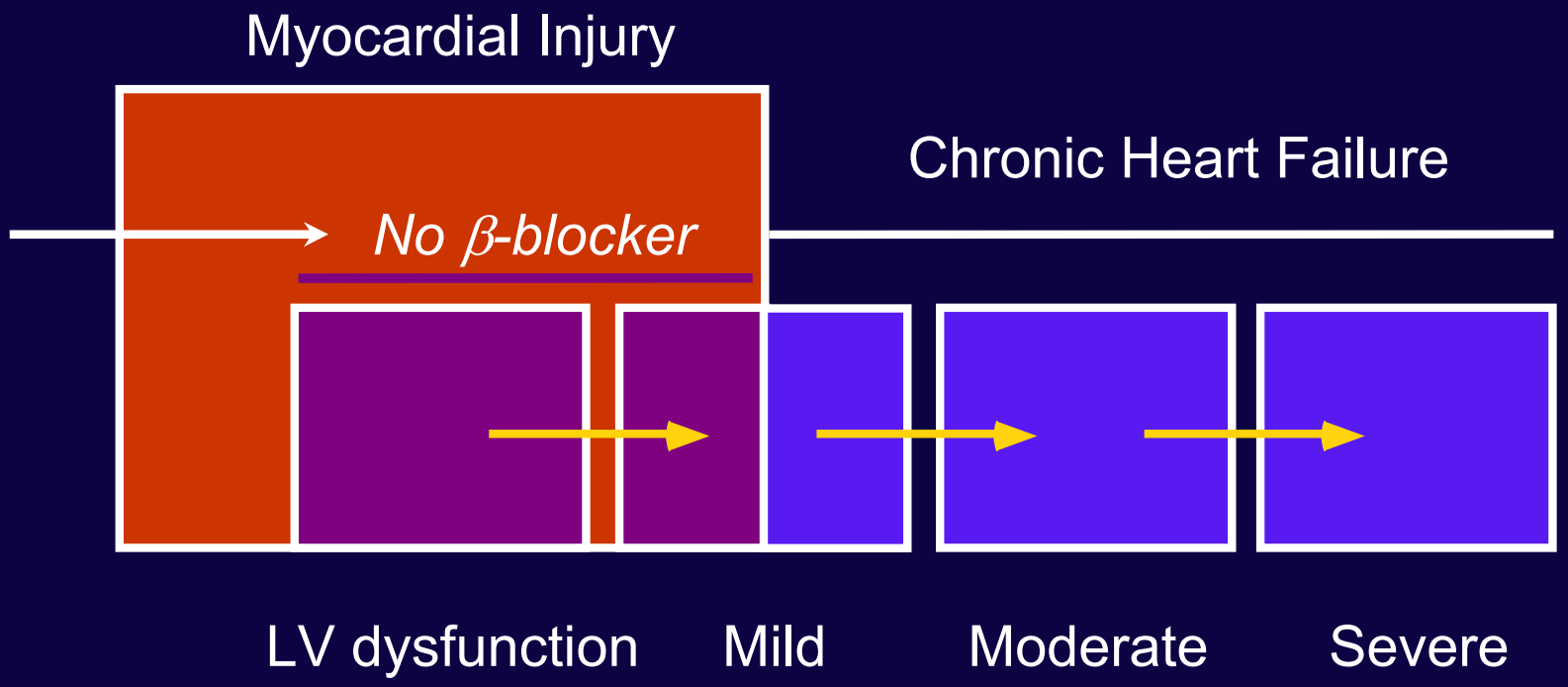
*Timolol, propranolol, metoprolol IR*



*Timolol, propranolol, metoprolol IR*

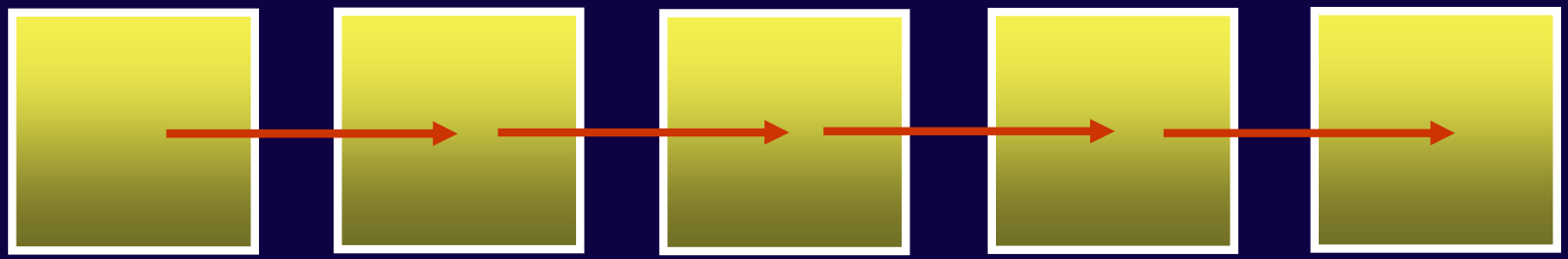


*Timolol, propranolol, metoprolol IR*



Recent Myocardial Infarction

Remote Myocardial Infarction



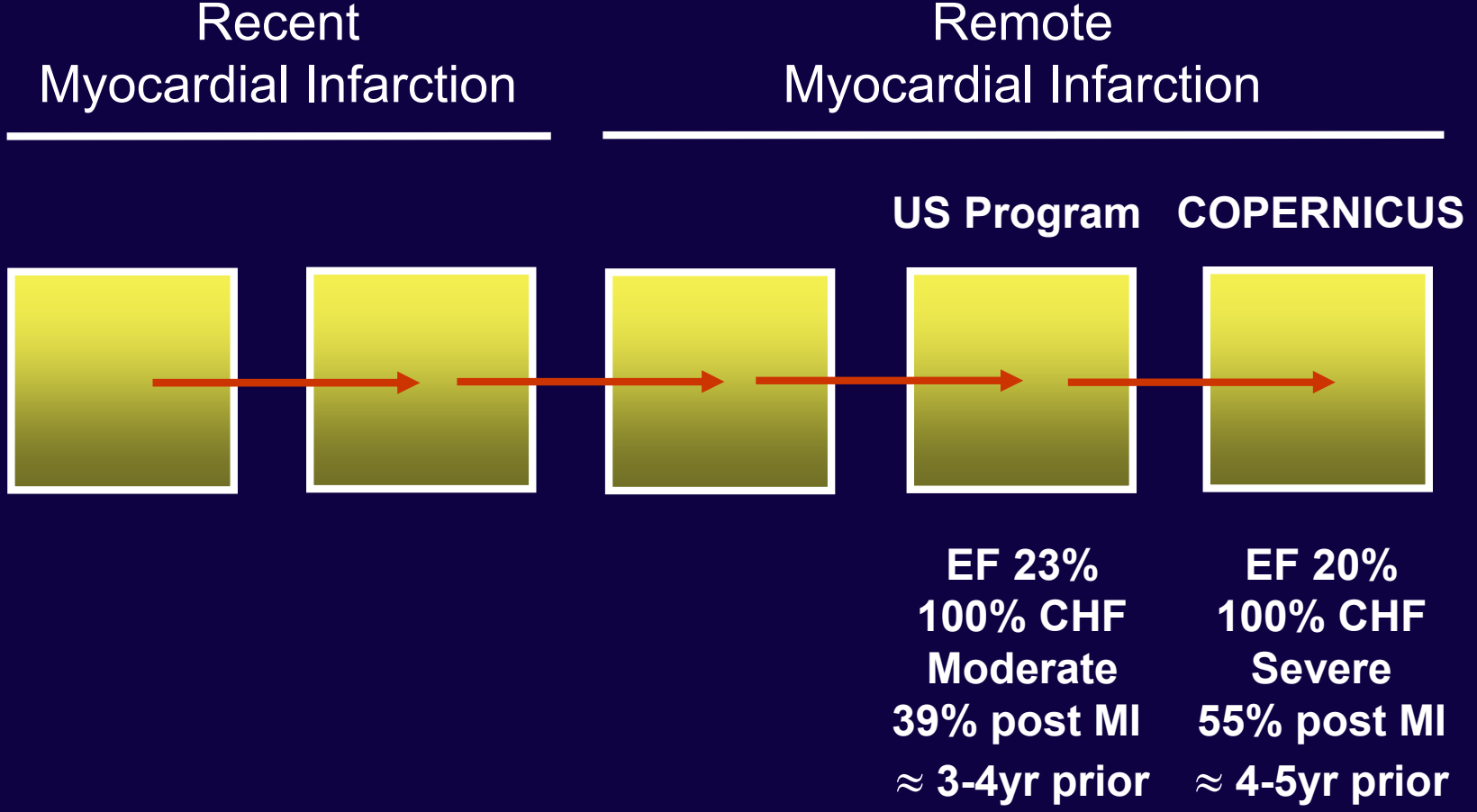
**Acute MI**

**Post-MI LV dysfunction**

**Mild CHF**

**Moderate CHF**

**Severe CHF**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EF 23%
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39% post MI
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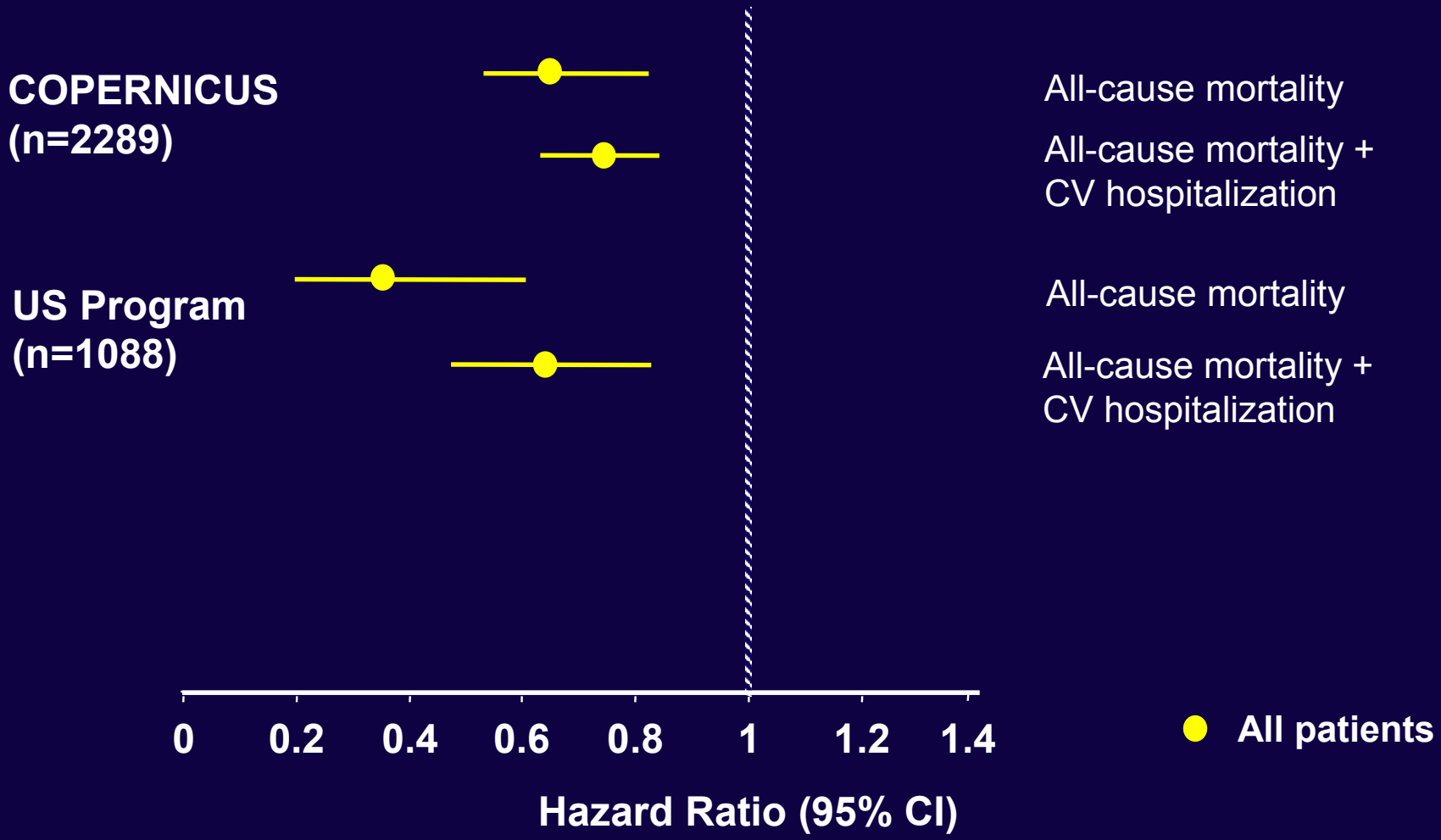
# *Effect of Carvedilol in Chronic Heart Failure With a Remote Myocardial Infarction*



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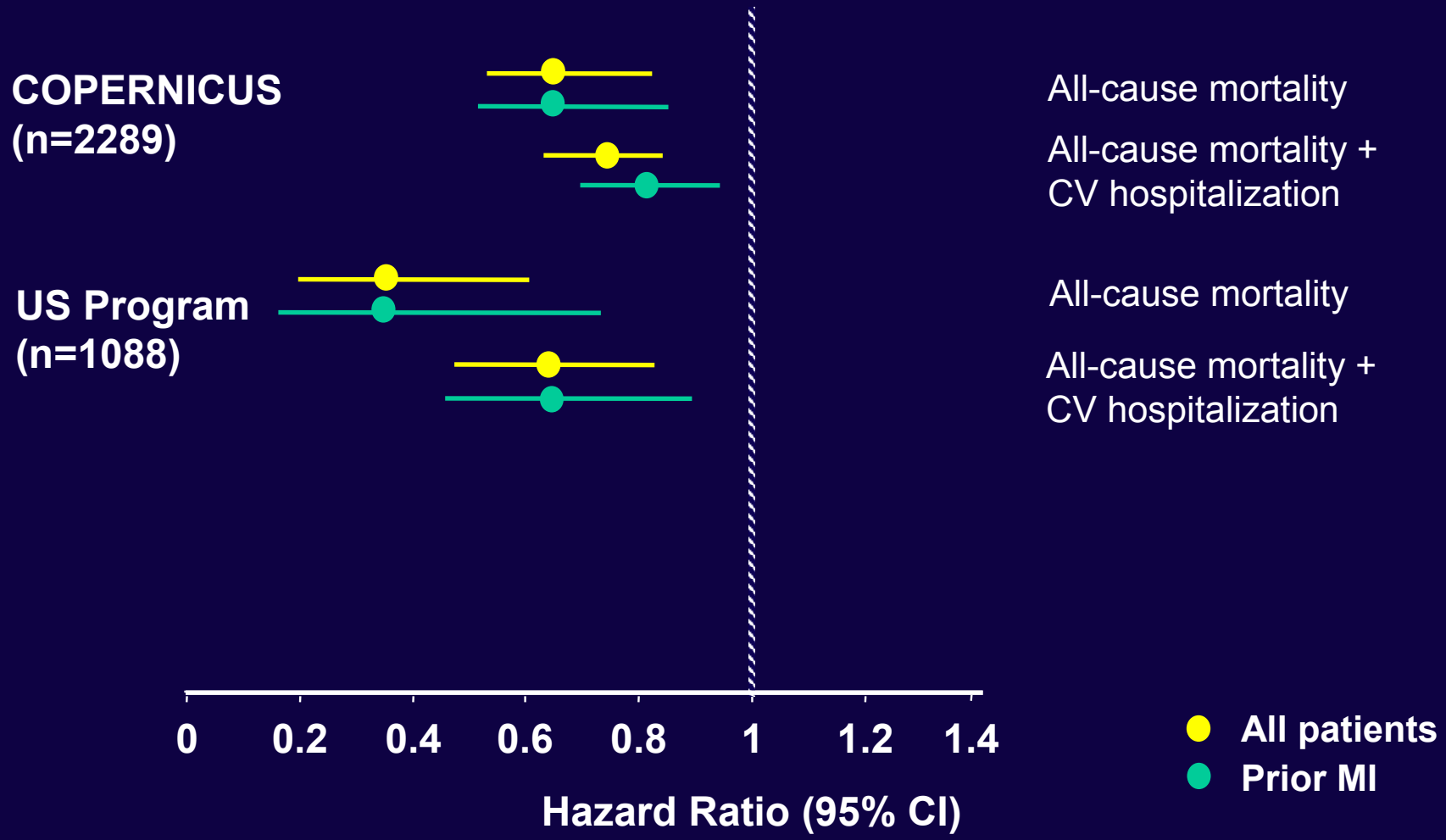

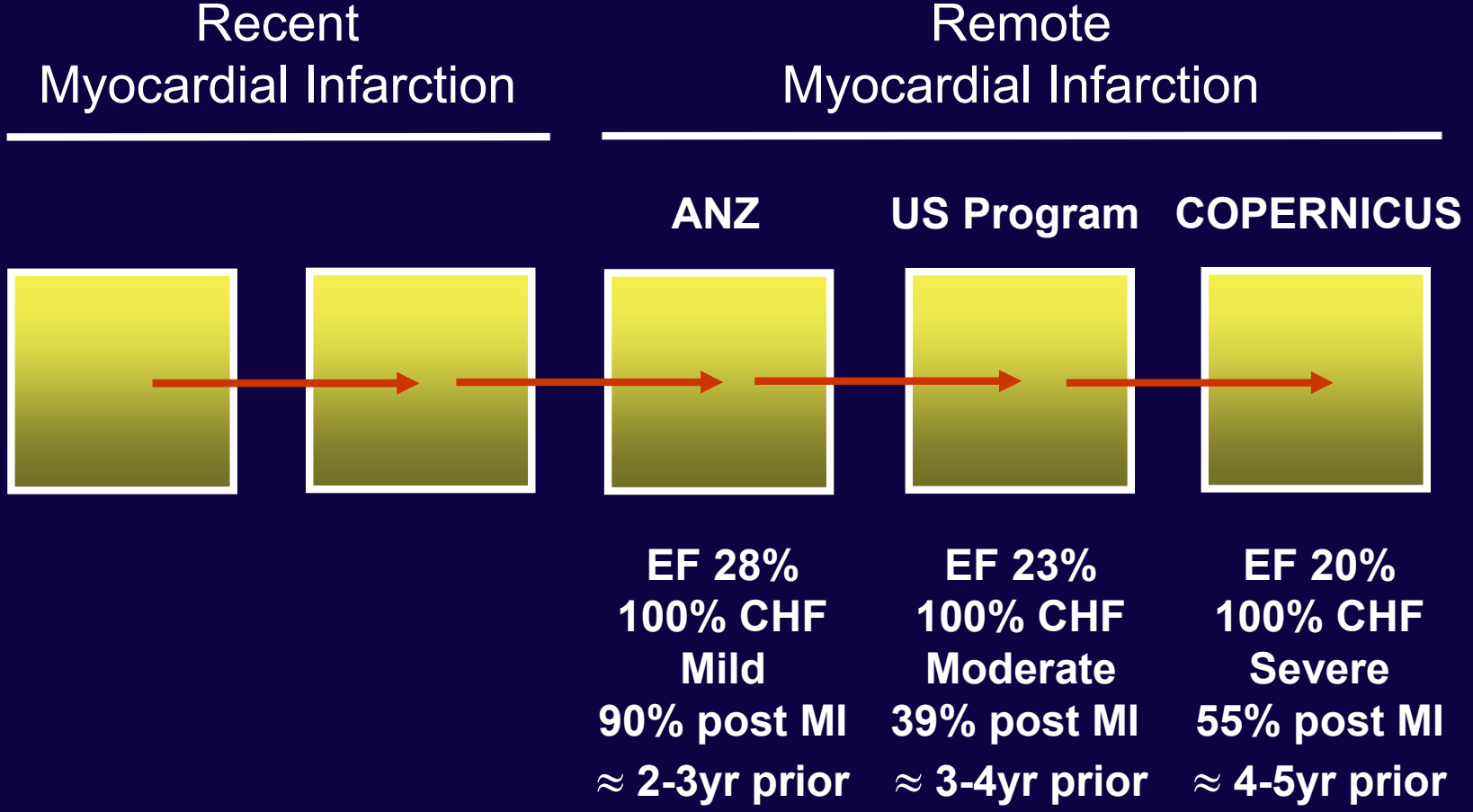
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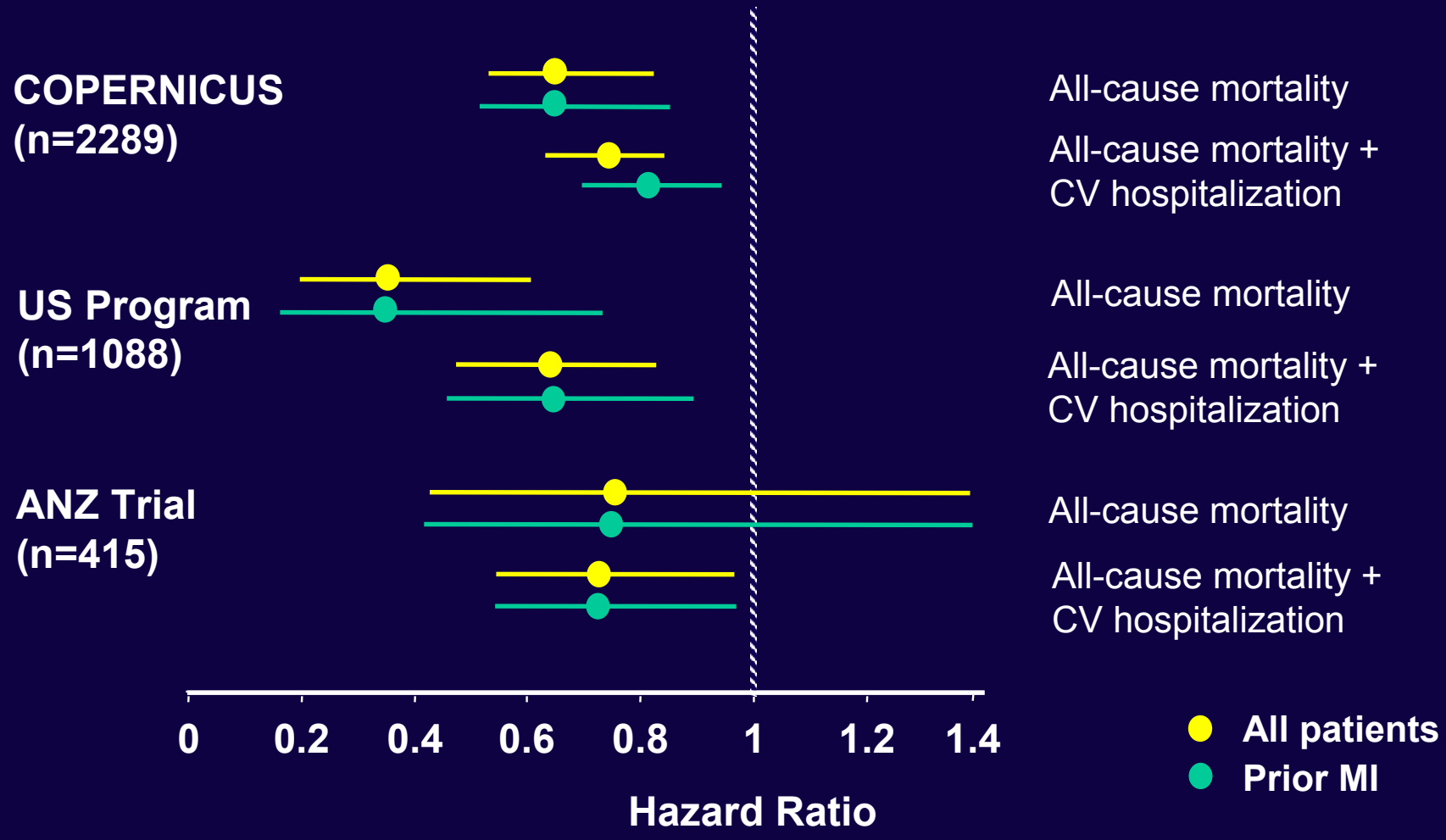

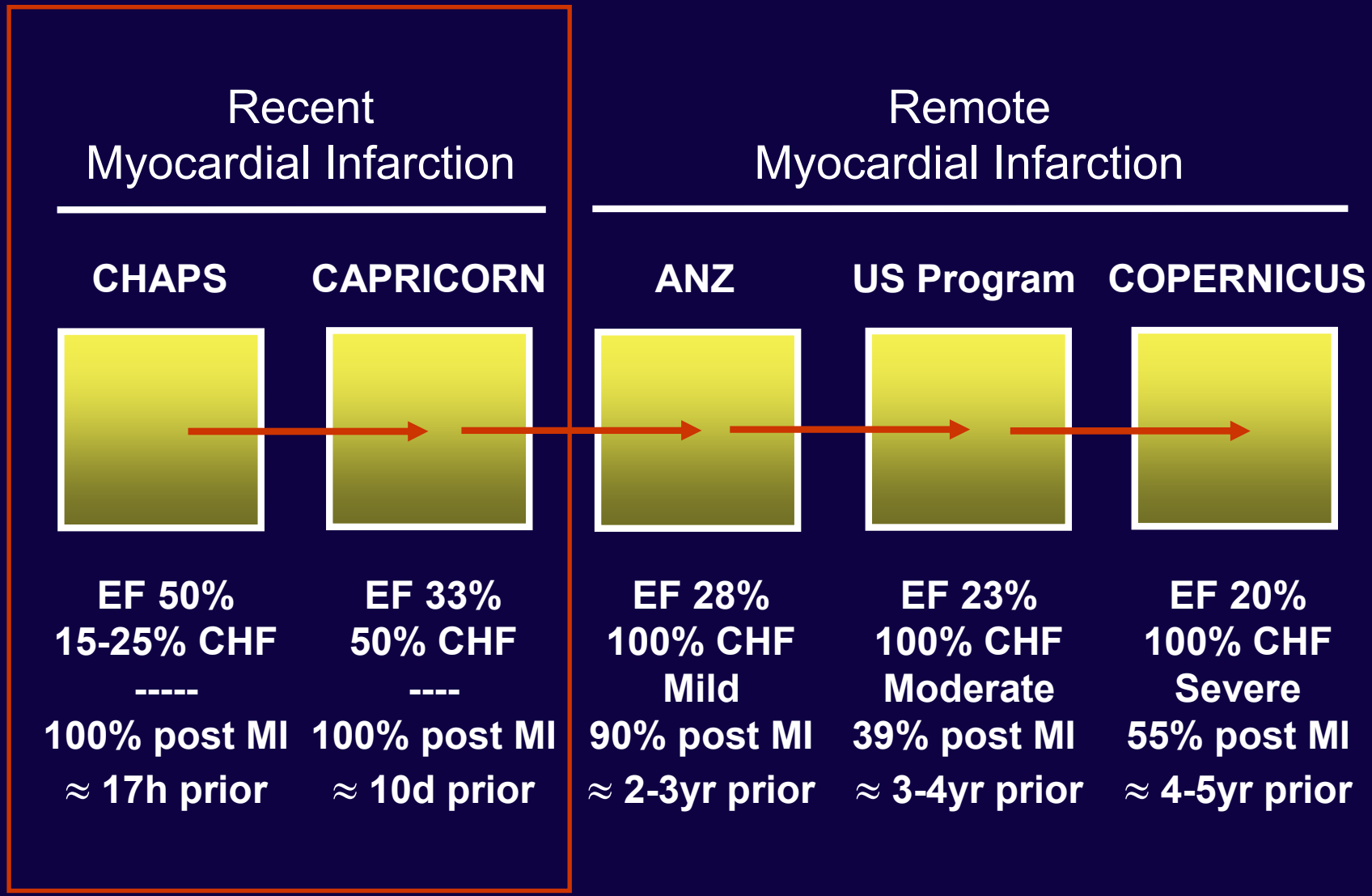
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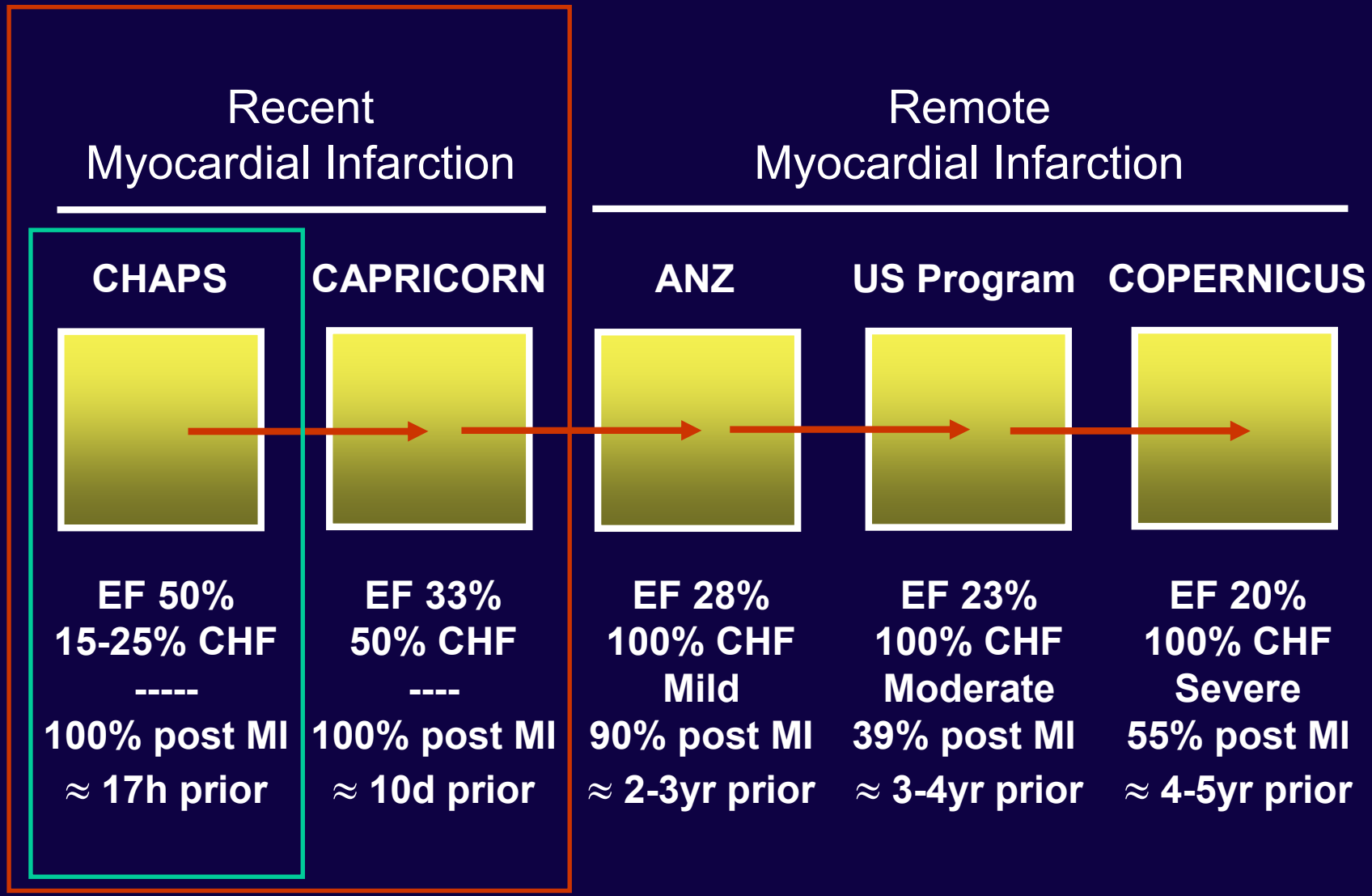
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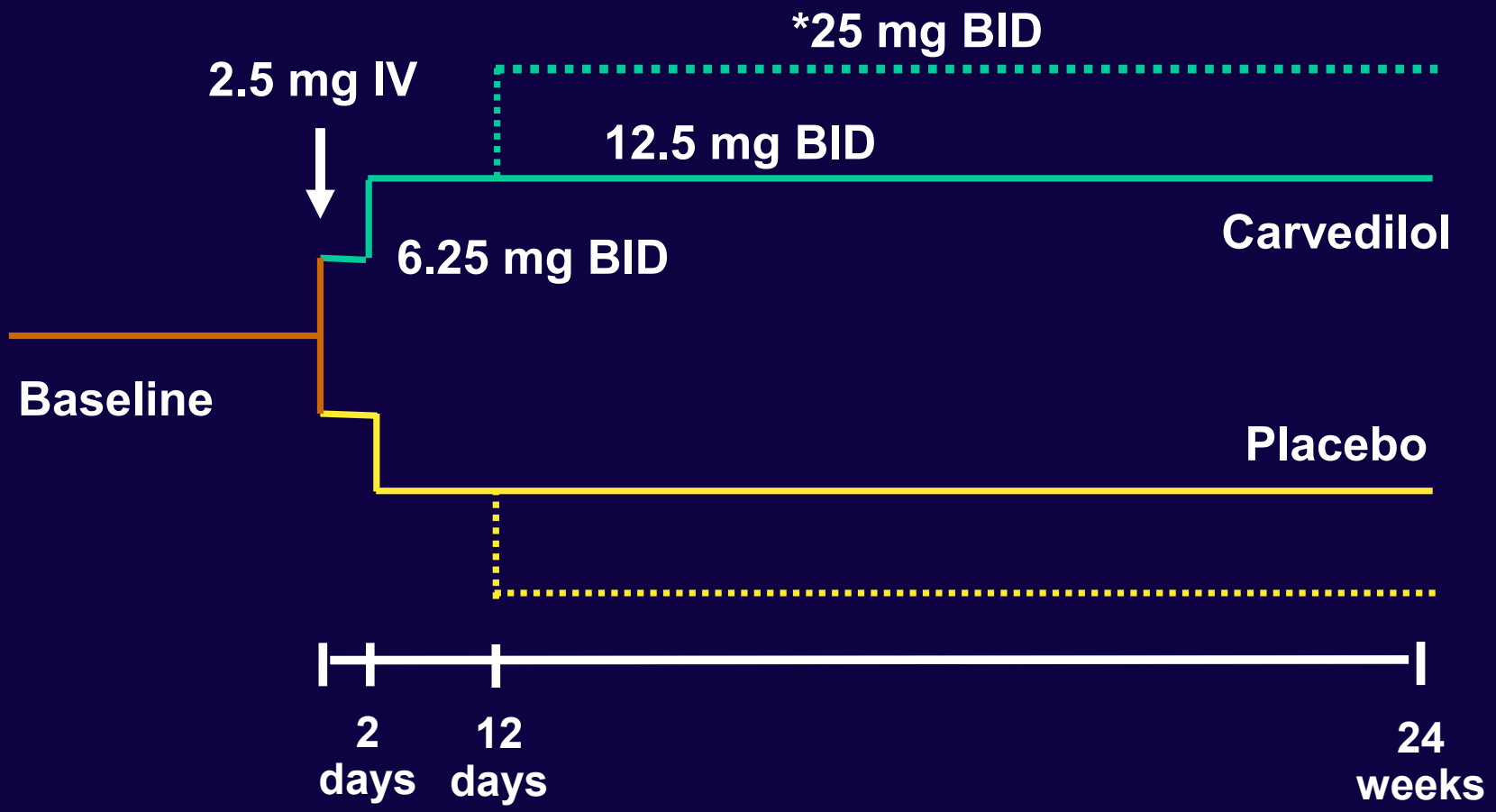
# *CHAPS: Inclusion and Exclusion Criteria*

- Acute myocardial infarction (chest pain, ECG changes and CK elevation) within 24 hours. Use of thrombolytics and aspirin was encouraged.

- Excluded if patient had bradycardia, heart block, systolic BP < 90, peripheral vascular disease, obstructive airways disease, insulin dependent diabetes or received beta-blocker prior to study entry.

# CHAPS: Study Design




*Titrated if SBP>120 mmHg, HR>55bpm

# *CHAPS: Primary Endpoint*

Time to one of the following:

- Cardiac death
- Heart failure
- Recurrent myocardial infarction or unstable angina
- Cerebrovascular accident
- Ventricular arrhythmia requiring medical therapy
- Emergency revascularization
- Use of a new cardiovascular drug (except for nitrates or diuretics within 72 hrs of onset of pain)

# *CHAPS: Patient Disposition*

- 151 patients randomized (74 placebo, 77 carvedilol)
- One patient (placebo) was withdrawn before receiving study drug. Four (2 in each group) did not have acute MI and had study drug withdrawn within 4 days
- 146 remaining patients were most commonly titrated to 12.5 mg BID (90% carvedilol, 73% placebo)
- Only 87 patients continued to receive study drug for 24 weeks. Most common reason for withdrawal was occurrence of primary endpoint.

# *CHAPS: Baseline Characteristics*

| | Placebo (n=71) | Carvedilol (n=75) |
|---|---|---|
| Age (years) | 60 | 60 |
| Sex (men/women) | 60/11 | 63/12 |
| History of hypertension | 24% | 9% |
| History of diabetes | 18% | 12% |
| Current smoker | 34% | 52% |
| History of MI before index MI | 4% | 3% |
| Site of index MI (% anterior) | 51% | 51% |
| Thrombolytic therapy for index MI | 96% | 99% |
| Aspirin therapy for index MI | 100% | 100% |
| IV heparin for index MI | 96% | 97% |
| Coronary vasodilators for index MI | 78% | 83% |
| Diuretics for heart failure post index MI | 11% | 25% |
| LV ejection fraction 48 hrs post randomization | 0.51 | 0.51 |
| Systolic BP (mm Hg) | 130 | 130 |
| Heart rate (beats/min) | 80 | 80 |
| Time from index MI to randomization (median) | 17.0 hours | 16.5 hours |

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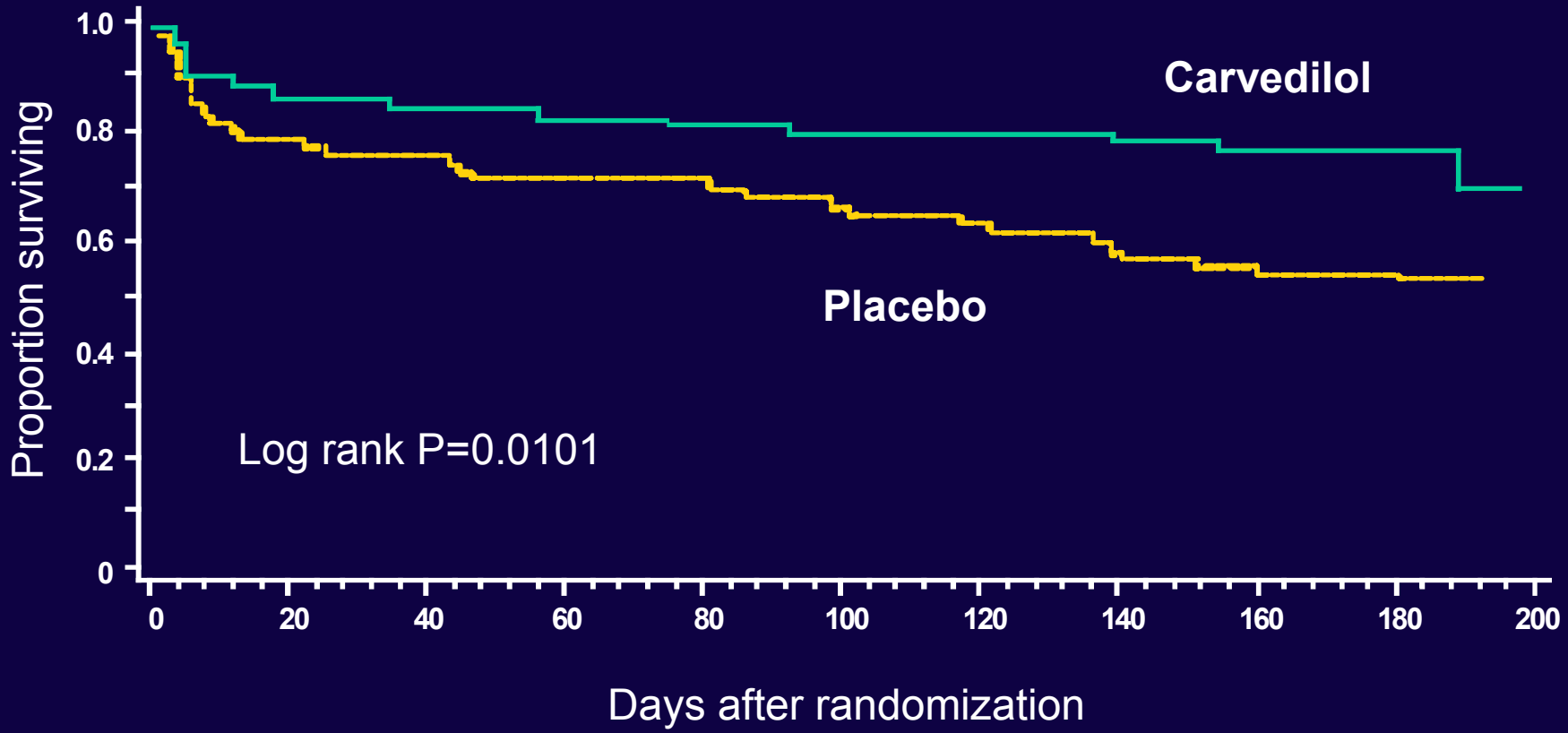
# *CHAPS: Primary Endpoint*

| | Placebo (n=71) | Carvedilol (n=75) |
|---|---|---|
| Cardiac death | 3 | 2 |
| Heart failure | 5 | 5 |
| Recurrent myocardial infarction | 8 | 4 |
| Unstable angina | 6 | 3 |
| Stroke | 1 | 0 |
| Emergent revascularization | 2 | 0 |
| Ventricular arrhythmia requiring IV treatment | 1 | 0 |
| New cardiovascular therapy | 5 | 4 |
| *Total number of patients* | 31 | 18 |

The new cardiovascular therapies were an ACE inhibitor for hypertension (n=1) and for a low ejection fraction (n=1) and a calcium antagonist for stable angina (n=3) in the placebo group and were a calcium antagonist for stable angina (n=2), an ACE inhibitor for worsening heart failure (n=1), and elective coronary artery bypass (n=1) in the carvedilol group.

# *CHAPS: Primary Endpoint*



# *CHAPS: Primary Endpoint (ITT Analysis)*

| | Primary Analysis | | Intention-to-Treat | |
|---|---|---|---|---|
| | **Placebo (n=71)** | **Carvedilol (n=75)** | **Placebo (n=73)** | **Carvedilol (n=77)** |
| Cardiac death | 3 | 2 | 3 | 2 |
| Heart failure | 5 | 5 | 5 | 5 |
| Recurrent infarction | 8 | 4 | 8 | 4 |
| Unstable angina | 6 | 3 | 6 | 4 |
| Stroke | 1 | 0 | 1 | 0 |
| Emergent CABG | 2 | 0 | 2 | 0 |
| Ventricular arrhythmia | 1 | 0 | 2 | 0 |
| New CV therapy | 5 | 4 | 5 | 4 |
| *Total number of patients* | 31 | 18 | 32 | 19 |
| *Log rank P value* | P=0.0101 | | P=0.0103 | |

# *CHAPS: Secondary Endpoint (Mortality)*

Placebo

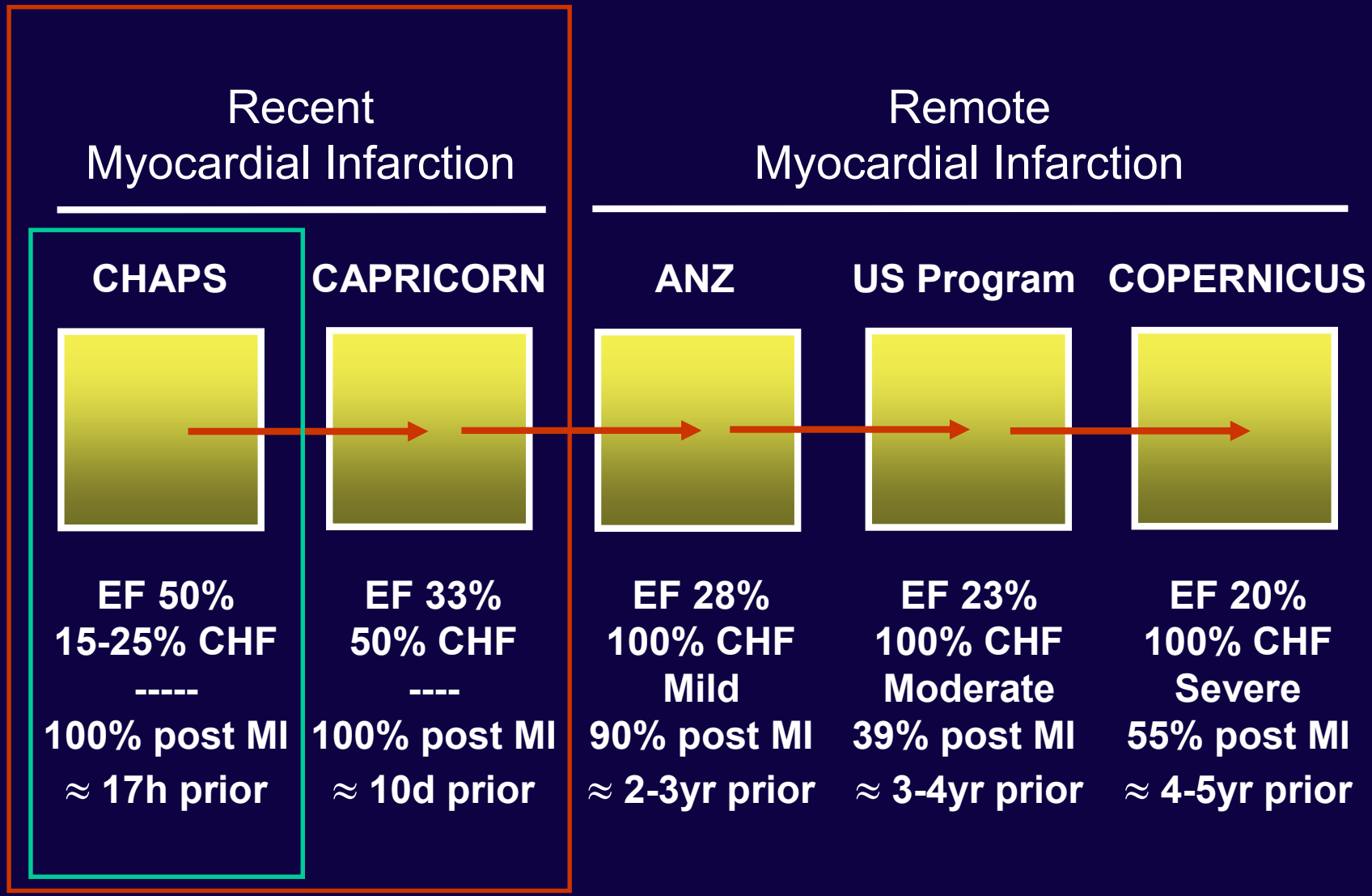
- 4 deaths (reinfarction in 2 and asystole in 2 [1 due to ventricular rupture]) occurring 1, 3, 26 and 56 days after randomization.

Carvedilol

- 2 deaths (electromechanical dissociation in 1 patient and asystole in 1 patient) occurring 2 and 78 days after randomization.

# *CHAPS*: *Summary*

- The CHAPS study supports ability of carvedilol to reduce the risk of death and reinfarction in post-infarction patients.
- The CHAPS study demonstrates the tolerability of carvedilol in immediate post-infarction period.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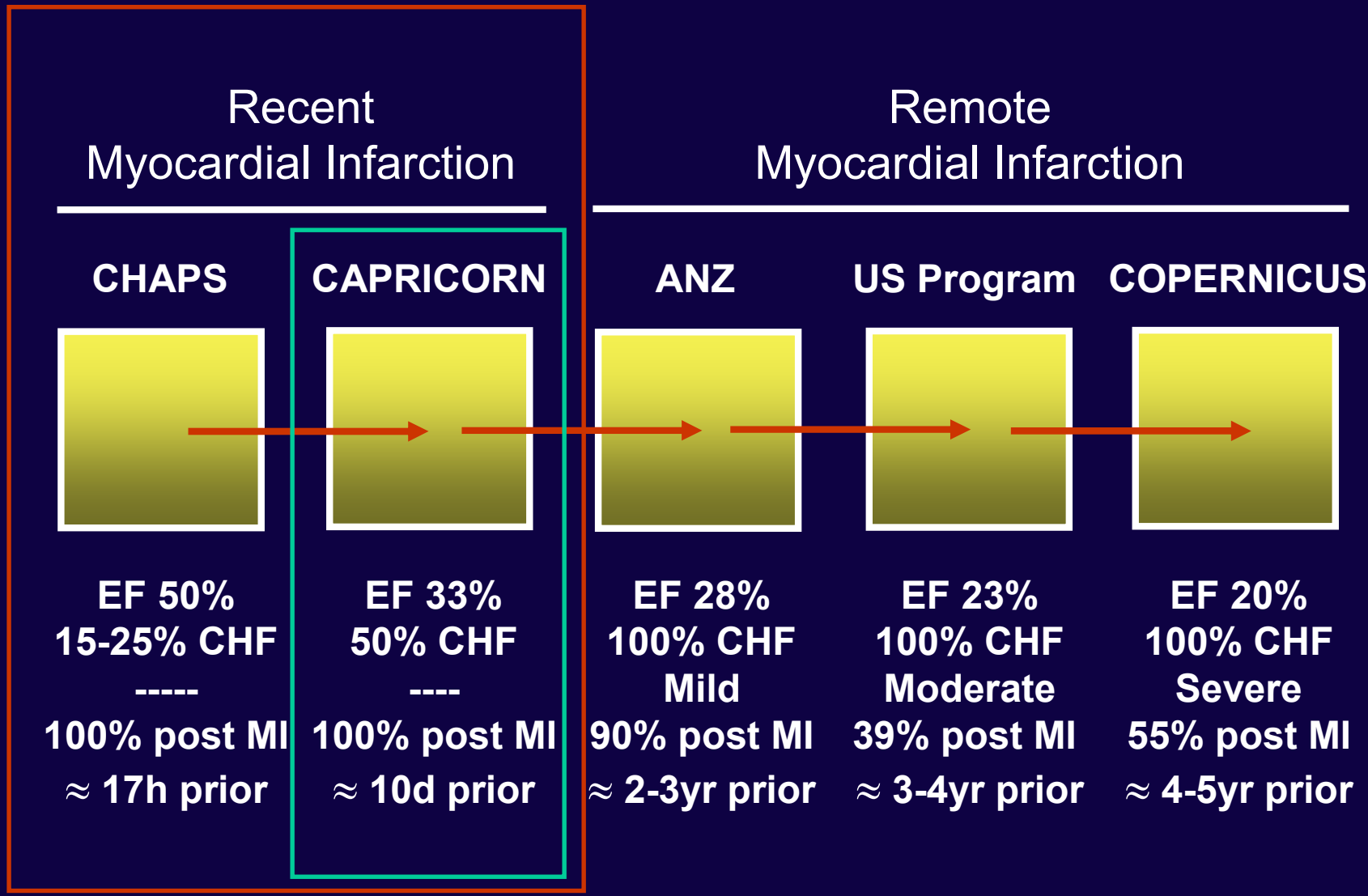
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# *Primary Results of the CAPRICORN Trial*

Henry Dargie, MB., ChB.

# *Objective/Study Design*

- To evaluate the effect of carvedilol on all-cause mortality in patients with LV dysfunction who have recently survived an acute myocardial infarction in the modern era
- Multicenter, randomized, placebo-controlled, parallel-group trial in patients with LV ejection fraction $\leq$ 40%, with or without heart failure
- Involved 163 centers in 17 countries (including those in Europe, Israel, North America, Australia, New Zealand)

# *Study Organization*

Steering Committee
H Dargie (UK), W Colucci (US), JL Lopez-Sendon (Es), W Remme (NL), N Sharpe (NZ)

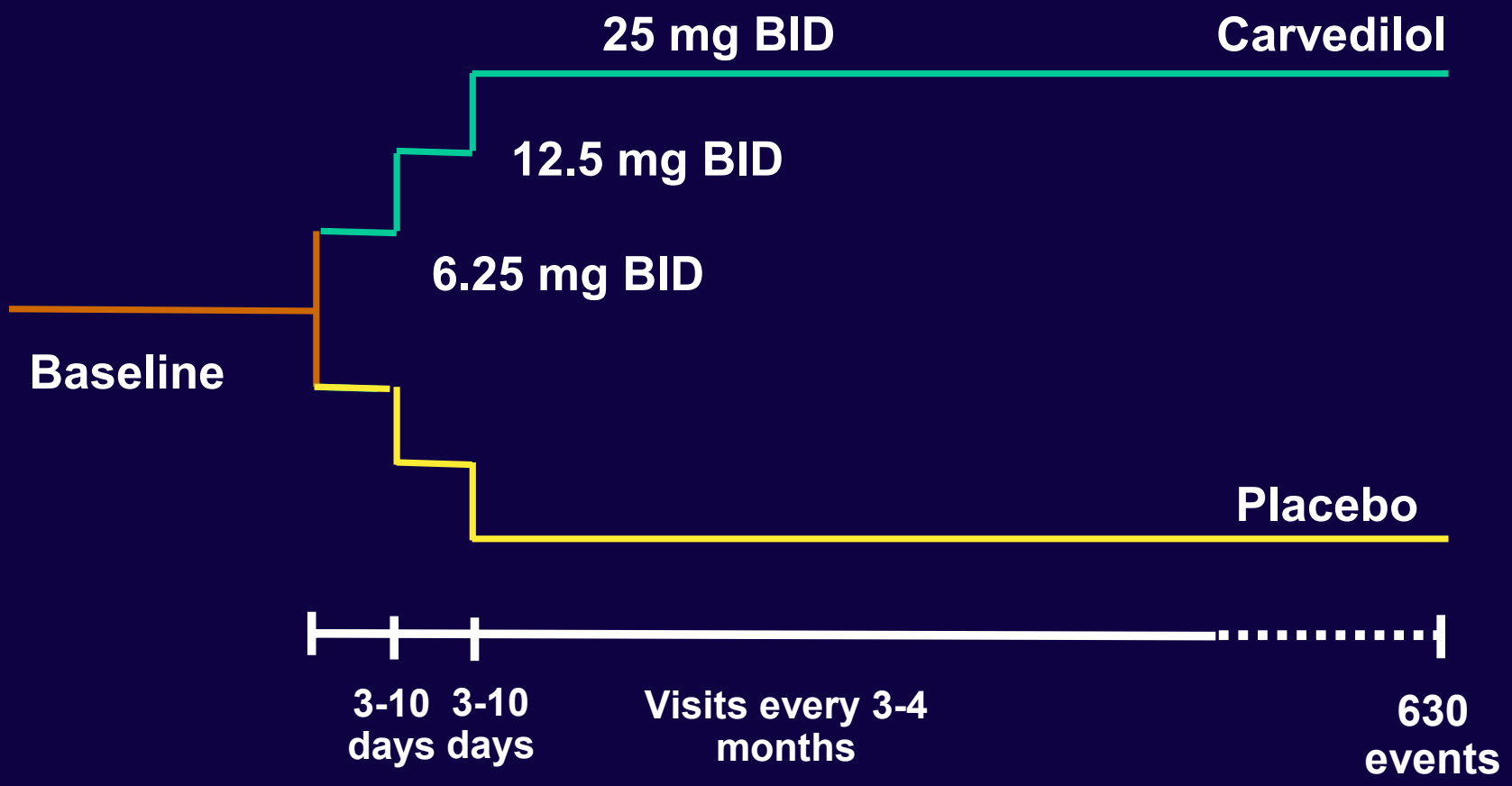
Endpoint Committee
J McMurray (UK) , L Kober (DK), J Sackner-Bernstein (US), J Soler-Soler (Es), F Zannad(F)

Data and Safety Monitoring Board
D Julian (UK), B Massie (US), S Thompson (UK), L Wilhelmson (DK), I Ford (UK)

# *Inclusion and Exclusion Criteria*

- Acute myocardial infarction within 21 days. Use of all adjunctive therapy was encouraged.
- LV ejection fraction $\leq$ 40% and receiving ACE inhibitor $\geq$ 48 hr; 80% hospitalized at time of study entry.
- Excluded if unstable angina, uncontrolled ventricular arrhythmias or hypertension, bradycardia, heart block, systolic BP < 90 mm Hg, obstructive airways disease, unstable diabetes or requiring inotropic therapy.
- Clinically stable but may have had pulmonary edema or cardiogenic shock during index infarction.

# Study Design



# *Protocol-Specified Endpoints*

- Primary Endpoint
  - All cause mortality
- Secondary Endpoints
  - All-cause mortality or CV hospitalization
  - Sudden death
  - Progression of heart failure

# Statistical Considerations

- Sample size was 2600 based on assumption that 21-month mortality would be 29% in the placebo group and that risk of death would be altered by 20% as a result of treatment with carvedilol (90% power, $\alpha$=0.05).
  - No allowance provided for open-label use of $\beta$-blockers.
- Trial was to continue until 630 patients had died with minimum follow-up of 12 months.
- All patients were to be followed until end of study whether they continued taking the study medication

# *DSMB Recommendation (March 1999)*

- Enrollment began June 1997. Based on findings of CIBIS II and MERIT-HF (announced in late 1998 and early 1999), DSMB believed that patients developing heart failure should be considered for β-blockade.
- Since high rate of open-label β-blocker use might compromise study and in view of a lower than anticipated mortality rate DSMB recommended adoption of a new endpoint to allow accelerated completion of study.
- DSMB recommendations made in March 1999 prior to any formal interim analysis of unblinded data.

# Response to DSMB Recommendations

| | Original Protocol | Amended Protocol |
|---|---|---|
| Projected number of patients | 2600 | 1850 |
| Use of open-label beta-blockers | Strongly discouraged | Actively considered |
| Primary endpoint(s) | All-cause mortality | All-cause mortality; all-cause mortality or CV hospitalization |
| Assignment of alpha | 0.05 to all-cause mortality | 0.005 to all-cause mortality; 0.045 for death or CV hospitalization |
| Secondary endpoints | 1. All-cause mortality or CV hospitalization<br>2. Sudden death<br>3. Progression of heart failure | 1. Sudden death<br>2. Hospitalization for heart failure |
| Target number of events | 630 deaths | 633 fatal or non-fatal events |
| Anticipated treatment effect | 20% | 23% |

# Baseline Characteristics

| | Placebo (n=984) | Carvedilol (n=975) |
|---|---|---|
| Age (years) | 63 | 63 |
| Sex (% men) | 74% | 73% |
| History of hypertension before index MI | 52% | 55% |
| History of angina before index MI | 54% | 57% |
| History of MI before index MI | 29% | 31% |
| ACE inhibitor use before index MI | 7% | 9% |
| Diabetes mellitus | 23% | 21% |
| Hyperlipidemia | 33% | 32% |
| β-Blocker use before index MI | 3% | 3% |
| Site of index MI (% anterior) | 55% | 59% |
| Typical cardiac pain during index MI | 94% | 95% |
| Pulmonary edema during index MI | 18% | 19% |
| ↑ Cardiac enzymes during index MI | 85% | 84% |

# Baseline Characteristics

| | Placebo (n=984) | Carvedilol (n=975) |
|---|---|---|
| Thrombolytic therapy for index MI | 37% | 36% |
| Primary coronary angioplasty for index MI | 13% | 12% |
| IV heparin for index MI | 65% | 63% |
| IV or other nitrate for index MI | 73% | 73% |
| IV β-blocker for index MI | 10% | 11% |
| Oral β-blocker for index MI | 32% | 31% |
| ACE inhibitor use before randomization | 97% | 98% |
| β-Blocker use before randomization | 35% | 33% |
| Aspirin use before randomization | 85% | 85% |
| Use of lipid lowering drugs before randomization | 24% | 22% |
| Heart failure prior to randomization | 47% | 48% |
| IV Diuretics for index MI | 33% | 35% |
| Systolic blood pressure (mm Hg) | 121 | 122 |
| Heart rate (beats/min) | 77 | 77 |
| Left ventricular ejection fraction | 33% | 33% |
| Days from index MI to randomization | 10.0 (range 1-30) | 10.0 (range 1-28) |

# *Patient Disposition*

- 1959 patients randomized (984 placebo, 975 carvedilol)
- Ten patients were randomized but did not receive the study drug (included in all analyses).
- Target doses achieved in 84% of placebo and 78% of carvedilol patients within 12 weeks and generally maintained for duration of study.
- Duration of follow-up: 3-33 months (mean 15 months)

# *Compliance with Study Medications*

| | Placebo | Carvedilol |
|---|---|---|
| Patients who permanently discontinued double-blind treatment | 231 | 237 |
| Patients who received open-label treatment with a β-blocker | 145 | 91 |
| Number of days until initiation of open label β-blocker | 269 | 329 |
| Number of days receiving open label β-blocker | 150 | 109 |

# *Results on Primary Endpoints*

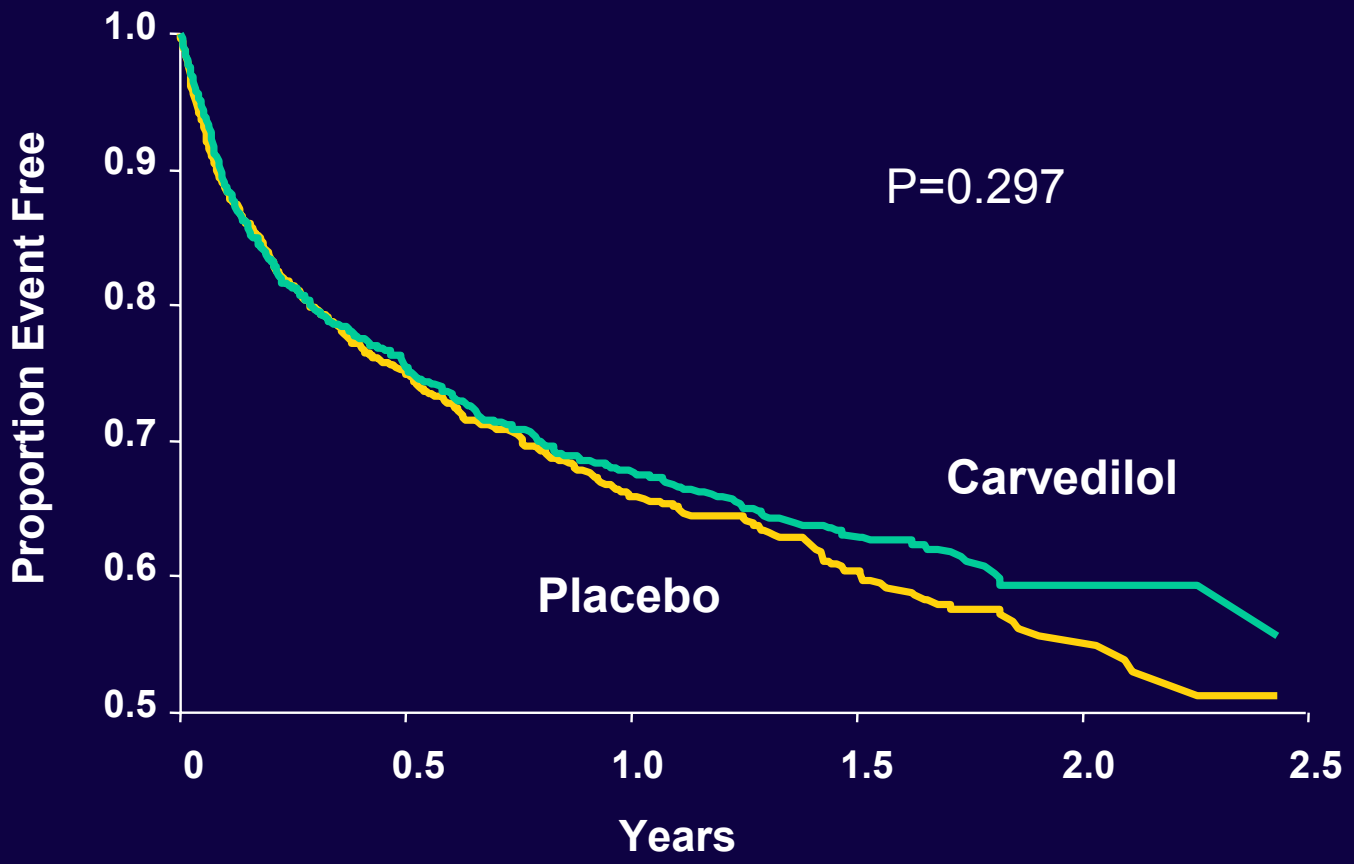
- All-cause mortality or cardiovascular hospitalization
- All-cause mortality

# *Co-Primary Endpoint*

| | Placebo | Carvedilol | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|
| All-cause mortality or cardiovascular hospitalization | 367/984 | 340/975 | 0.92 (0.80-1.07) | 0.297 |

Amended protocol $\alpha$=0.045

# Death or Cardiovascular Hospitalization





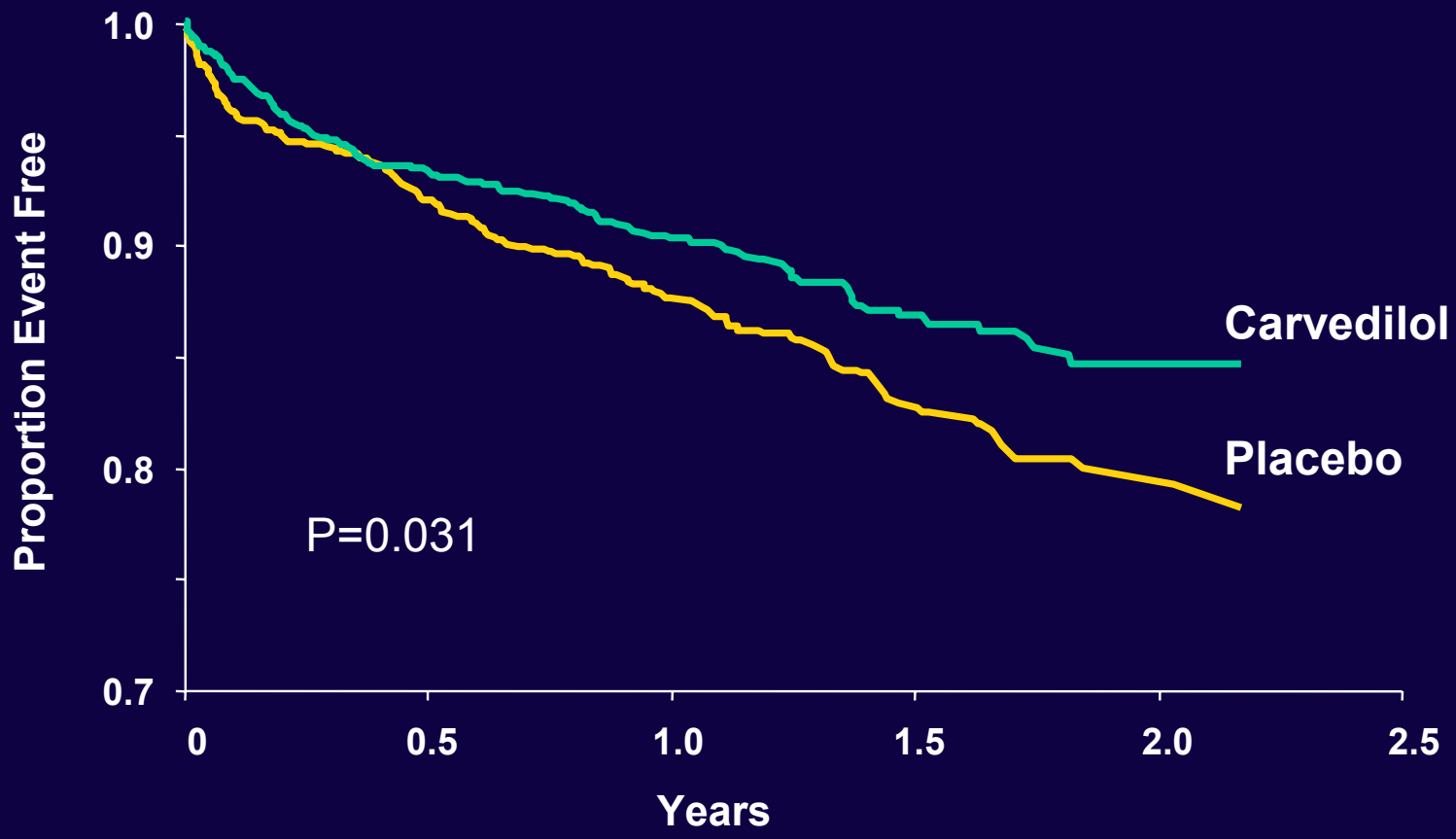

*The CAPRICORN Investigators, Lancet 2001*

# *Co-Primary Endpoint*

| | Placebo | Carvedilol | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|
| All-cause mortality | 151/984 | 116/975 | 0.77 (0.60-0.98) | 0.031 |

Amended protocol $\alpha$=0.005
($\alpha$=0.004 after adjustment for a single interim analysis)

# All-Cause Mortality






*The CAPRICORN Investigators, Lancet 2001*

# *Why Are We Here?*

Milton Packer, M.D.

# *Critical Questions to the Committee*

- Can the findings from a trial that did NOT meet its primary endpoint be used as the primary basis for labeling?
- If so, what criteria should the data supporting such a finding fulfill to justify incorporation into labeling?

# *Drugs Approved Based on the Results of Trials That Did Not Achieve Primary Endpoint*

**Digoxin (Lanoxin®)**

- Indicated for treatment of mild-to-moderate heart failure to reduce heart failure-related hospitalizations.
- The trial that observed this benefit (DIG) did not achieve its primary endpoint (all-cause mortality), P=0.80.

# *Drugs Approved Based on the Results of Trials That Did Not Achieve Primary Endpoint*

**Enalapril (Vasotec®)**

- Indicated for treatment of clinically stable asymptomatic patients with LV dysfunction (EF < 35%) to decrease the rate of development of overt CHF and decrease the incidence of hospitalizations for heart failure.
- The trial that observed this benefit (SOLVD Prevention) did not achieve its primary endpoint (all-cause mortality, P=0.30).

# *Critical Questions to the Committee*

- Can the findings from a trial that did NOT meet its primary endpoint be used as the primary basis for labeling?

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- Can the findings from a trial that did NOT meet its primary endpoint be used as the primary basis for labeling?
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# *What Rules Should Guide the Decision to Allow the Inclusion of a "Discovery" Into Labeling?*

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- The criteria that would allow inclusion of a "discovery" into labeling should have strength of evidence comparable to that which would allow labeling based on a trial or trials that achieved their primary endpoints.

# *What Rules Should Guide the Decision to Allow the Inclusion of a "Discovery" Into Labeling?*

- The criteria that would allow inclusion of a "discovery" into labeling should have strength of evidence comparable to that which would allow labeling based on a trial or trials that achieved their primary endpoints.
- Do such criteria allow one to conclude that carvedilol reduces mortality in post-infarction patients with LV dysfunction?

# *Death is a Unique Endpoint*

- The finding of a reduction in the risk of death associated with treatment is always compelling, since death is an unbiased endpoint of paramount clinical importance.

- FDA review: "FDA has acted as if all clinical trials implicitly have $\alpha$=0.05 assigned to an analysis of mortality, independent of the primary end point."

# *Do All Trials Have $\alpha$=0.05 Assigned to Mortality?*

| | | Control | Drug | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|---|
| Vesnarinone (vs placebo) | Initial study | 33/238 | 13/239 | 0.38 (0.20-0.72) | 0.002 |
| | Definitive study | 242/1283 | 292/1275 | 1.22 (1.04-1.42) | 0.02 |
| Losartan (vs captopril) | Initial study | 32/370 | 17/352 | 0.54 (0.31-0.95) | 0.035 |
| | Definitive study | 250/1574 | 280/1578 | 1.13 (0.95-1.35) | 0.16 |

# *CAPRICORN*

- The mortality effect seen in CAPRICORN was not a accidental “discovery”.
- The CAPRICORN Trial was designed specifically to evaluate the effect of carvedilol on mortality.
- Large number of events (n=267) with high annual placebo mortality rate (12.1%).

# *Original Intent of the CAPRICORN Trial*

| | **Original Protocol** | **Final Results** |
|---|---|---|
| Main objective | Evaluate all-cause mortality | Evaluate all-cause mortality |
| Level of statistical significance | $\alpha$=0.05 to all-cause mortality | P=0.03 for all-cause mortality |
| Treatment effect | 20% anticipated | 23% observed |

# *CAPRICORN*

- The mortality effect seen in CAPRICORN was not a accidental “discovery”.
- The CAPRICORN Trial was designed specifically to evaluate the effect of carvedilol on mortality.
- Large number of events (n=267) with high annual placebo mortality rate (12.1%).
- Mortality effects seen in the CAPRICORN trial have been replicated in (rather than contradicted by) other post-infarction β-blocker trials.

# *Do All Trials Have an Implicit $\alpha$ Assigned to the Analysis of Mortality?*

- Even if one assumes that all trials implicitly have an $\alpha$=0.05 assigned to mortality, how persuasive is the P=0.031 observed for the mortality effect of carvedilol in the CAPRICORN trial?

- The $\alpha$=0.005 assigned to mortality in CAPRICORN set an extremely high standard of reproducibility — achieved by one trial with a very small P value or two or more trials with P < 0.05.

# *β-Blockers Shown to Reduce Mortality in a Large-Scale Controlled Clinical Trial*

- Timolol
- Metoprolol
- Propranolol
- Acebutolol
- Practolol

# *Effect on Mortality of β-Blockers Approved for Post-Infarction Patients*

| Study Name | Treatment Groups | Average duration of f/u | # Patients Who Died | | P value |
|---|---|---|---|---|---|
| | | | Placebo | β–Blocker | |
| Norwegian Timolol Study | Placebo (n=939)<br>Timolol (n=945) | 17 months | 152 | 98 | < 0.001 |
| β-Blocker Heart Attack Trial | Placebo (n=1921)<br>Propranolol (n=1916) | 25 months | 188 | 138 | < 0.01 |
| Göteborg Metoprolol Trial | Placebo (n=697)<br>Metoprolol (n=698) | 3 months | 62 | 40 | = 0.03 |
| Lopressor Inter-vention Trial | Placebo (n=1200)<br>Metoprolol (n=1195) | 18 months | 93 | 86 | NS |

# *Meta-Analysis of Effect of β-Blockers on Mortality in Earlier Post-Infarction Trials*

| | **Earlier Post-MI β-Blocker Trials** |
|---|---|
| All-cause mortality | 0.77 (0.69, 0.85) |

Based on 2415 deaths in 24,974 patients enrolled in 31 trials

Sources: Freemantle et al, Br Med J 1999; 318:1730-7

# *Comparison of Results of CAPRICORN With Earlier Post-MI β-blocker Trials*

| Study Name | Treatment Groups | Average duration of f/u | # Patients Who Died | | P value |
|---|---|---|---|---|---|
| | | | Placebo | β–Blocker | |
| Norwegian Timolol Study | Placebo (n=939)<br>Timolol (n=945) | 17 months | 152 | 98 | < 0.001 |
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| Lopressor Inter-vention Trial | Placebo (n=1200)<br>Metoprolol (n=1195) | 18 months | 93 | 86 | NS |
| CAPRICORN Trial | Placebo (n=984)<br>Carvedilol (n=975) | 15 months | 151 | 116 | = 0.03 |

# *Comparison of Results of CAPRICORN With Earlier Post-MI β-blocker Trials*

| | CAPRICORN Trial | Earlier Post-MI β-Blocker Trials |
|---|---|---|
| All-cause mortality | 0.77 (0.60, 0.98) | 0.77 (0.69, 0.85) |

Sources: Freemantle et al, Br Med J 1999; 318:1730-7

# *Comparison of Results of CAPRICORN With Earlier Post-MI β-blocker Trials*

| | CAPRICORN Trial | Earlier Post-MI β-Blocker Trials | Heart Failure in Earlier Post-MI β-Blocker Trials |
|---|---|---|---|
| All-cause mortality | 0.77 (0.60, 0.98) | 0.77 (0.69, 0.85) | 0.79 (0.65, 0.96) |

17 trials noted LV dysfunction or CHF, which was present in 22% of patients

Sources: Freemantle et al, Br Med J 1999; 318:1730-7
Houghton et al, Eur J Heart Failure 2000; 2:333-40

# *Is It Appropriate To Consider the Results of Other Post-Infarction β-Blocker Trials?*

# *Is It Appropriate To Consider the Results of Other Post-Infarction β-Blocker Trials?*

## Angiotensin Antagonists in Diabetic Nephropathy

- The Committee expressed skepticism about approvability of losartan based on a single trial — in the absence of other evidence.

# *Is It Appropriate To Consider the Results of Other Post-Infarction β-Blocker Trials?*

Angiotensin Antagonists in Diabetic Nephropathy

- The Committee expressed skepticism about approvability of losartan based on a single trial — in the absence of other evidence.
- The Committee recommended approval when findings in the losartan trial were considered together with the highly concordant findings of a similar trial with irbesartan in the same disease — a trial which when considered alone did not lead the Committee to recommend approval of irbesartan.

# *Is It Appropriate To Consider the Results of Other Post-Infarction β-Blocker Trials?*

Assumption Underlying Class Effect

- The Committee believed that neither losartan nor irbesartan had effects that might detract from their ability as angiotensin antagonists to prevent the progression of renal disease.
- Does carvedilol have effects that might detract from its actions as a beta-blocker to reduce mortality in the post-infarction setting?

# *Relation of Pharmacological Properties of β-Blockers and Effect of Survival in Post-Infarction Trials*

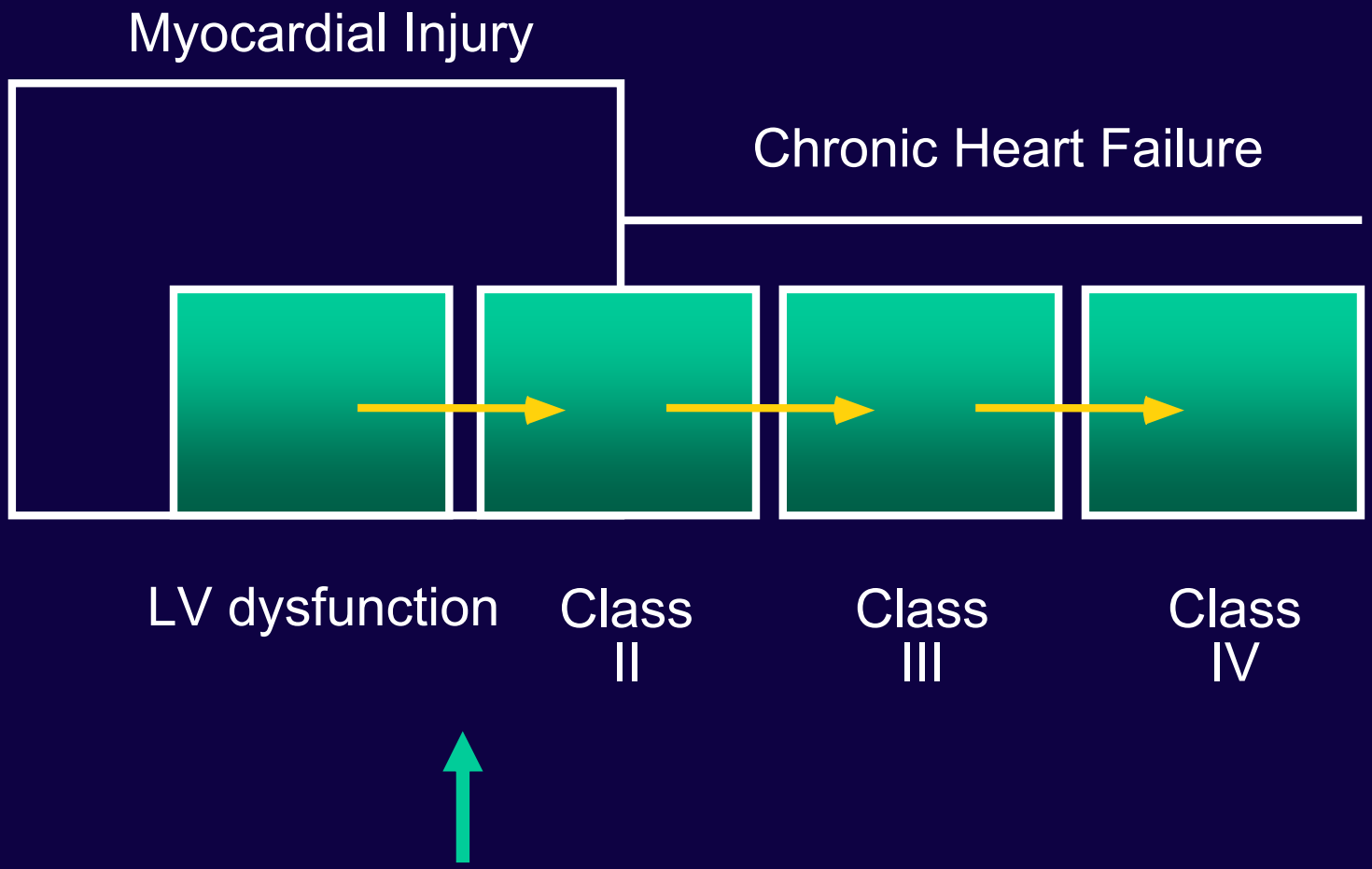
| Drug | β-1 receptor blockade | Cardio-selective | Intrinsic sympatho-mimetic activity | Odds ratio vs placebo (95%CI) |
|---|---|---|---|---|
| Timolol | + | — | — | 0.59 (0.46-0.77) |
| Propranolol | + | — | — | 0.71 (0.59-0.85) |
| Sotalol | + | — | — | 0.80 (0.54-1.21) |
| Metoprolol | + | + | — | 0.80 (0.66-0.96) |
| Practolol | + | + | + | 0.80 (0.63-1.02) |
| Alprenolol | + | — | + | 0.83 (0.59-1.17) |
| Oxprenolol | + | — | + | 0.91 (0.71-1.17) |
| Pindolol | + | — | + | 0.96 (0.60-1.55) |
| All β-blockers | | | | 0.77 (0.69-0.85) |

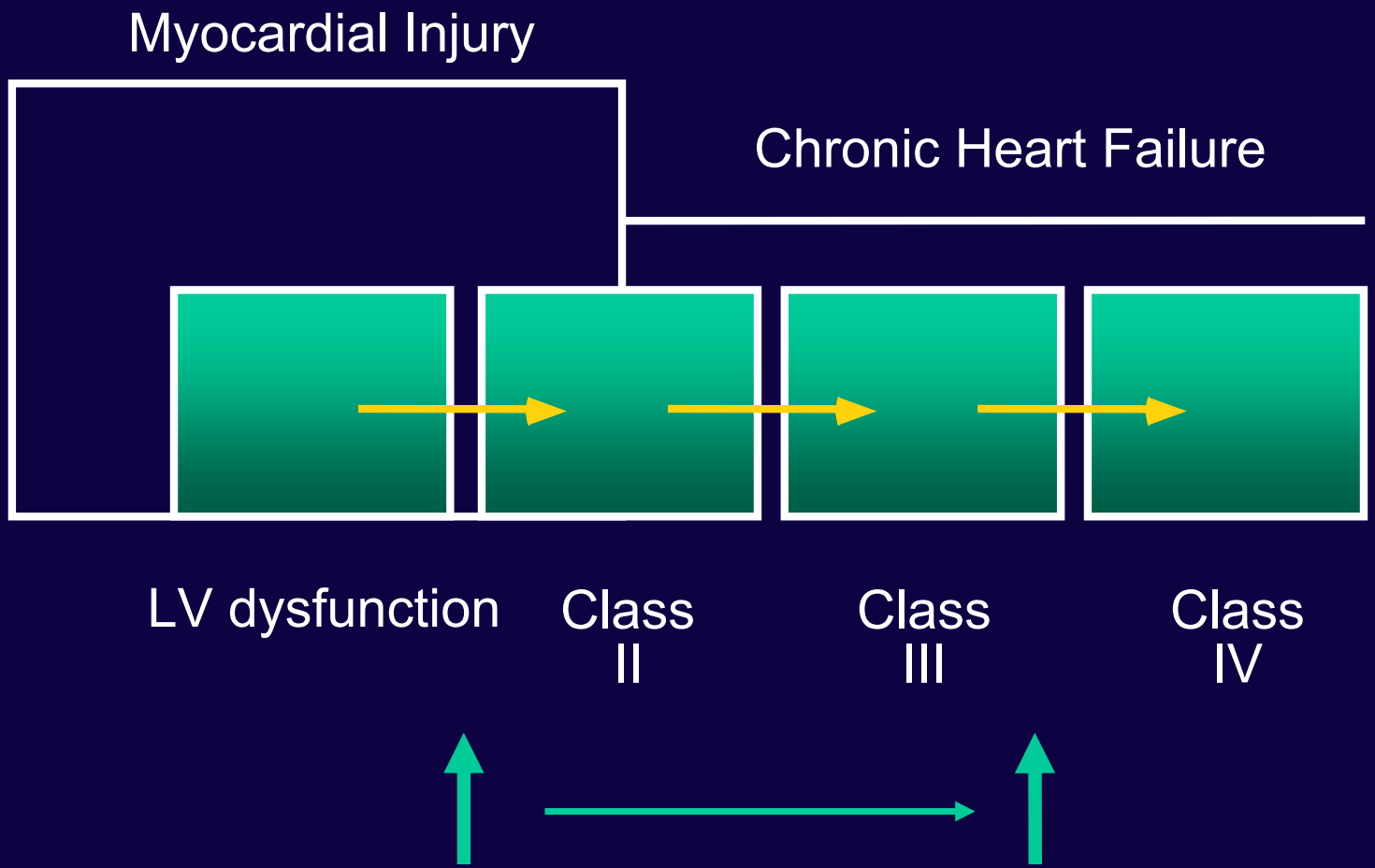
Included in this table are all β-blockers that have been evaluated in placebo-controlled trials that enrolled (collectively) more than more than 75 deaths. Drugs are listed in order of increasing odds ratios. Data are from Freemantle et al.

# *Relation of Pharmacological Properties of β-Blockers and Effect of Survival in Post-Infarction Trials*

| Drug | β-1 receptor blockade | Cardio-selective | Intrinsic sympatho-mimetic activity | Odds ratio vs placebo (95%CI) |
|---|---|---|---|---|
| Timolol | + | — | — | 0.59 (0.46-0.77) |
| Propranolol | + | — | — | 0.71 (0.59-0.85) |
| **Carvedilol** | **+** | **—** | **—** | **0.74 (0.57-0.95)** |
| Sotalol | + | — | — | 0.80 (0.54-1.21) |
| Metoprolol | + | + | — | 0.80 (0.66-0.96) |
| Practolol | + | + | + | 0.80 (0.63-1.02) |
| Alprenolol | + | — | + | 0.83 (0.59-1.17) |
| Oxprenolol | + | — | + | 0.91 (0.71-1.17) |
| Pindolol | + | — | + | 0.96 (0.60-1.55) |
| All β-blockers | | | | 0.77 (0.69-0.85) |

Treatment effect of carvedilol includes the results of both CHAPS and CAPRICORN and is expressed as odds ratio rather than relative risk to be consistent with the approach used to estimate the treatment effect for other β-blockers. Data for other β -blockers are from Freemantle et al.


Myocardial Injury
Chronic Heart Failure
LV dysfunction
Class II
Class III
Class IV


Myocardial Injury
Chronic Heart Failure
LV dysfunction
Class II
Class III
Class IV

# *Relation of Pharmacological Properties of β-Blockers and Effect of Survival in Chronic Heart Failure Trials*

| Study Name | Treatment Groups (# of patients) | Hazard ratio for mortality (95% CI): All Patients | Hazard ratio for mortality (95% CI): Prior MI |
|---|---|---|---|
| CIBIS II | Placebo (n=1320)<br>Bisoprolol (n=1327) | 0.66 (0.54-0.81)<br>P < 0.001 | 0.60 (0.45-0.80) |
| MERIT-HF | Placebo (n=2001)<br>Metoprolol (n=1990) | 0.66 (0.53-0.81)<br>P < 0.001 | 0.60 (0.45-0.80) |
| COPERNICUS | Placebo (n=1133)<br>Carvedilol (n=1156) | 0.65 (0.52-0.81)<br>P < 0.001 | 0.61 (0.45-0.83) |
| BEST | Placebo (n=1354)<br>Bucindolol (n=1354) | 0.90 (0.78-1.02)<br>P = 0.13 | 0.95 (0.80-1.10) |
| Xamoterol Severe Heart Failure Study | Placebo (n=164)<br>Xamoterol (n=352) | 2.54 (1.04-6.18)<br>P = 0.02 | Not evaluated |

# *Is It Appropriate To Consider the Results of Other Post-Infarction β-Blocker Trials?*

- Long-term blockade of β-adrenergic receptors can be expected to reduce mortality in post-infarction patients.
- Drugs classified as β-blockers can exert effects that may detract from their ability as β-blockers to reduce mortality, and current approaches are able to detect such effects.
- The pharmacological properties of β-blockers that may diminish their survival effects appear to be similar in the post-infarction setting and in chronic heart failure.
- The observed effects of carvedilol in both post-MI patients and in chronic CHF indicate that the drug does not exert effects that detract from its action as a β-blocker to prolong life.

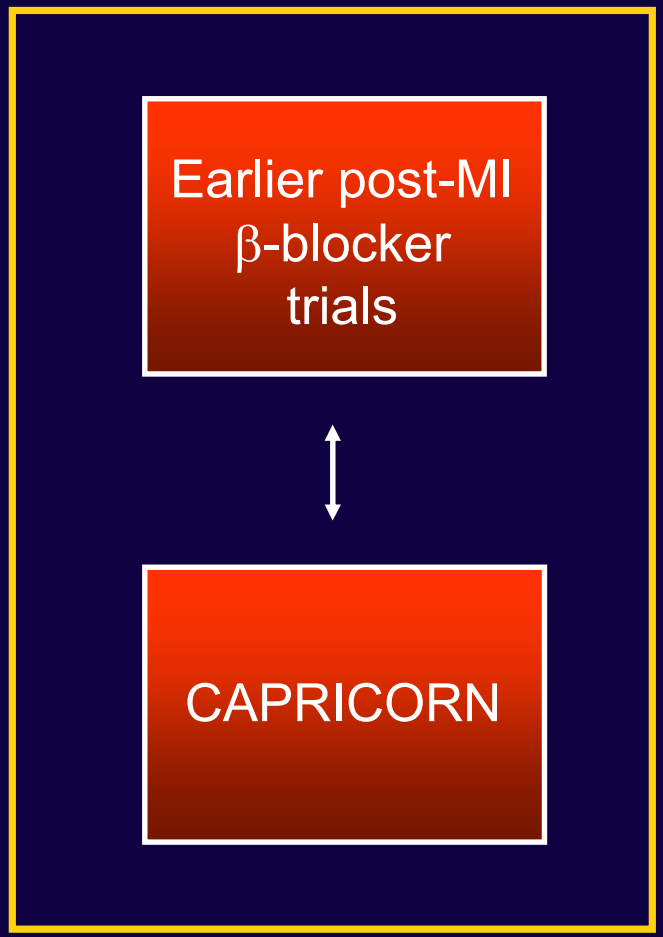
# *The Critical Question*

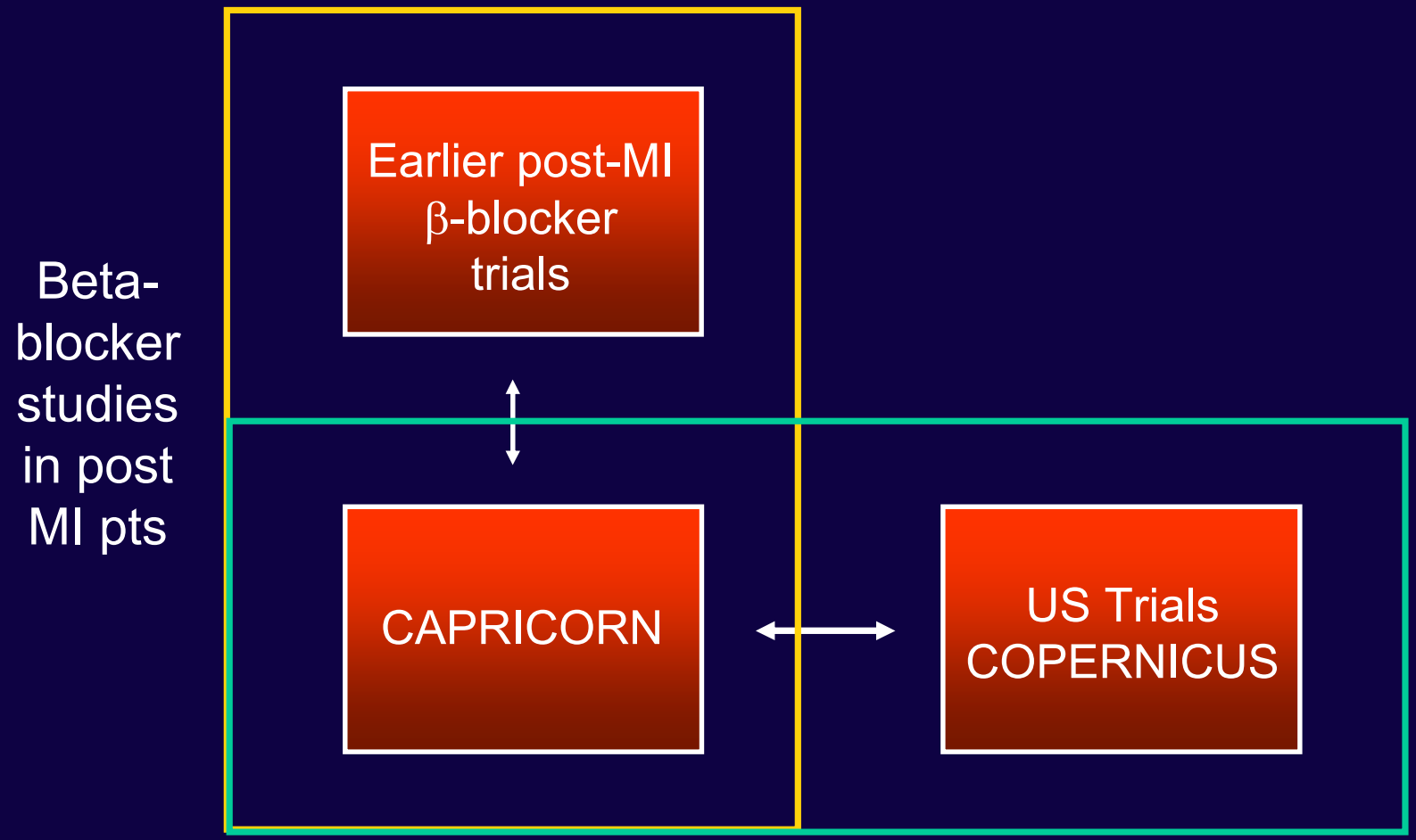
Is the totality of available data sufficiently credible and persuasive to conclude that carvedilol reduces mortality in the post-infarction patient with LV dysfunction?

CAPRICORN

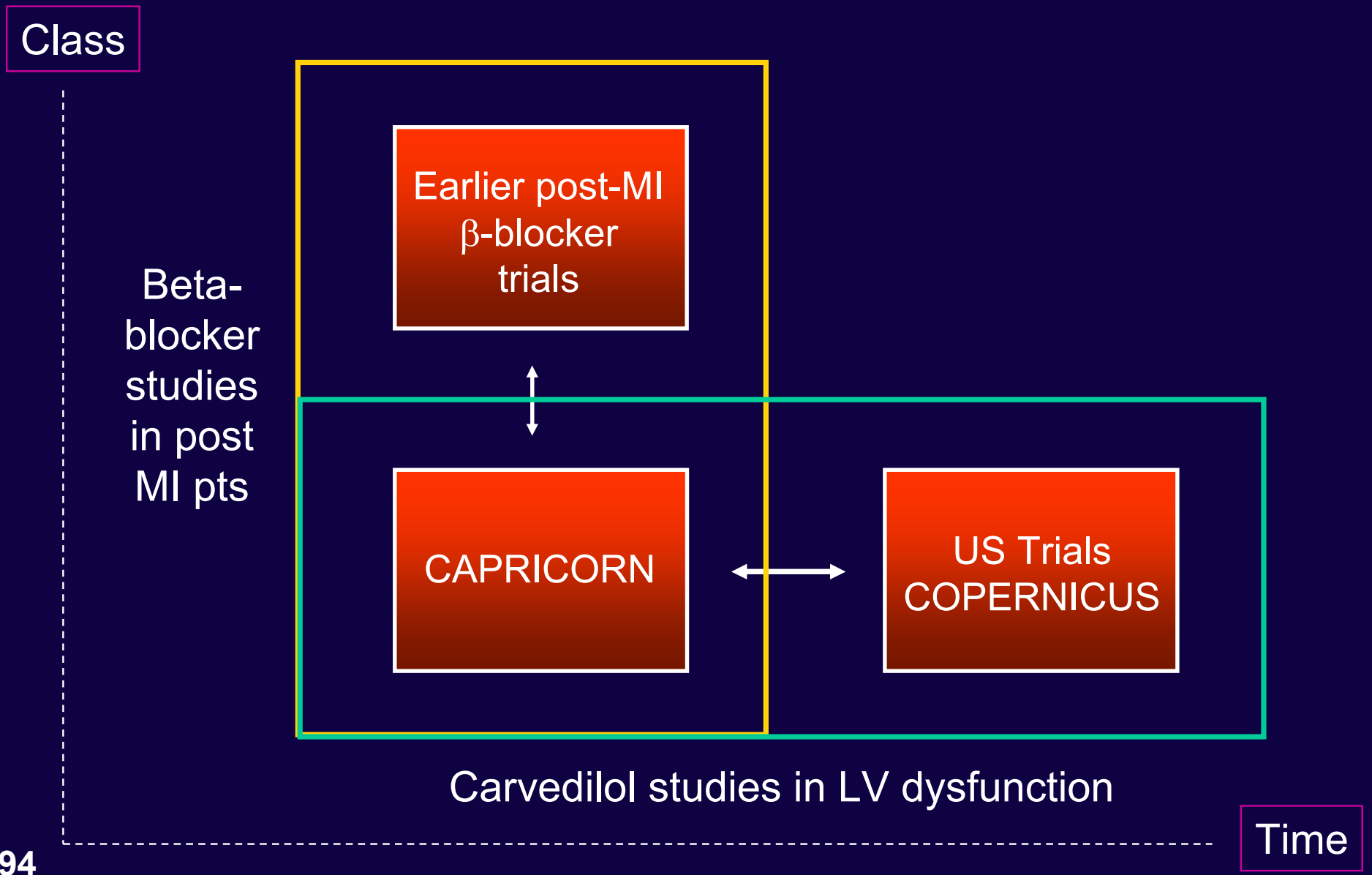
Mortality reduction
of anticipated magnitude seen
in trial designed to find it

Beta-blocker studies in post MI pts






Carvedilol studies in LV dysfunction on top of ACE inhibitor


Class
Beta-blocker studies in post MI pts
Earlier post-MI β-blocker trials
CAPRICORN
US Trials COPERNICUS
Carvedilol studies in LV dysfunction
Time

# *What Rules Should Guide the Decision to Allow the Inclusion of a "Discovery" Into Labeling?*

# *What Rules Should Guide the Decision to Allow the Inclusion of a "Discovery" Into Labeling?*

- **Finding should be a reduction in all-cause mortality in a trial designed to detect the finding**
- **Magnitude of the benefit anticipated by the protocol**
- **Observed magnitude of benefit both clinically relevant and realistic, with conclusions about benefit based on a meaningful number of events**
- **Substantial evidence of a similar benefit (both in nature and magnitude) in the same disease state with other members of the same class of drug**
- **Substantial evidence that the drug produces the same benefit later in the same disease, with comparable magnitude of benefit to that with other members of the class**
- **Support within the trial by additional evidence of clinical benefits without overriding safety concerns**

# *Question to the Committee*

- How much are you willing to allow an increase in the false positive rate by accepting data in a clinical trial that missed its primary endpoint?

# *Question to the Committee*

- How much are you willing to allow an increase in the false positive rate by accepting data in a clinical trial that missed its primary endpoint?
- In making regulatory decisions based on trials that missed their primary endpoints — can one reduce the false positive rate to acceptable levels, given the opportunity to consider not just the results of one trial but the totality of available data?  If so, how?

# *Effect of Carvedilol on Non-Fatal Events in the CAPRICORN Trial*

Henry Dargie, MB., ChB.

# *Comparison With Earlier Post-MI Trials*

| | CAPRICORN Trial | Earlier Post-MI β-Blocker Trials |
|---|---|---|
| All-cause mortality | 0.77 (0.60, 0.98) | 0.77 (0.69, 0.85) |
| All-cause mortality or CV hospitalization | 0.92 (0.80, 1.07) | ? |

Source: Freemantle et al, Br Med J 1999; 318:1730-7

# Components of Endpoint of Death or CV Hospitalization

| | Placebo (n=984) | Carvedilol (n=975) |
|---|---|---|
| Death | 78 | 65 |
| Hospitalization due to non-fatal myocardial infarction | 45 | 27 |
| Hospitalization due to worsening heart failure | 102 | 97 |
| Hospitalization due to unstable angina | 37 | 40 |
| Hospitalization due to cardiac arrhythmia | 25 | 8 |
| Hospitalization due to stroke or TIA | 12 | 12 |
| Hospitalization due to other angina or chest pain | 42 | 57 |
| Hospitalization for other cardiovascular reason | 26 | 34 |
| Total | 367 | 340 |

Results based on blinded adjudication by the Endpoint Committee and post hoc identification of admissions for a cardiac arrhythmia. Hospitalizations with > 1 cause were counted only once and attributed to the worst event (MI > CHF > stroke > TIA > supraventricular or ventricular arrhythmia > unstable angina > other angina or chest pain > other). Admissions for chest pain not due to a MI or unstable angina was attributed to “other angina”, unless there was a reason to suspect otherwise.

# *Endpoints Used in Other Post-MI β-Blocker Trials*

| | Non-Mortality CV Endpoint | Other Reported Events |
|---|---|---|
| **Norwegian Timolol Trial** | Nonfatal recurrent MI | ↑ CHF, ↑ hypotension, ↑ dizziness, ↑ bradycardia, ↑ peripheral vascular symptoms, ↓ arrhythmias |
| **Göteborg Metoprolol Trial** | Nonfatal recurrent MI, arrhythmias | ↑ hypotension, ↑ bradycardia, ↑ heart block |
| **Beta-Blocker Heart Attack Trial** | Nonfatal recurrent MI | ↑ early CHF, ↑ hypotension, ↑ peripheral vascular symptoms, ↓ arrhythmias |
| **Lopressor Intervention Trial** | None | ↑ hypotension, ↑ bradycardia, ↓ arrhythmias |

# *Effect of Propranolol on Cardiovascular Events Other Than Reinfarction in the BHAT Trial*

| | Placebo | Propranolol |
|---|---|---|
| Heart failure | 11.6% | 12.6% |
| Angina | 38.2% | 39.0% |
| Claudication | 11.6% | 11.3% |
| Stroke | 1.6% | 1.5% |

Source: JAMA 183; 250:2814-2819

# *Endpoints in Other LV Dysfunction Trials*

| | Target Patients | Non-Mortality CV Endpoint |
|---|---|---|
| SAVE (captopril) | Post-MI LVD | CV death or hospitalization for MI or CHF |
| AIRE (ramipril) | Post-MI CHF | Death or recurrent MI, severe resistant CHF or stroke |
| TRACE (trandolapril) | Post-MI LVD | (1) recurrent MI; (2) progression to severe CHF |
| EPHESUS (eplerenone) | Post-MI CHF | Death or hospitalization for MI, CHF, stroke or arrhythmia |
| PRAISE (amlodipine) | LVD + CHF | Death or hospitalization for MI, CHF, ventricular arrhythmia |
| COPERNICUS (carvedilol) | LVD + CHF | Death or hospitalization for MI or unstable angina, CHF, stroke or TIA, atrial or ventricular arrhythmia, bradycardia or heart block |

# *Effect on Cardiovascular Endpoints*

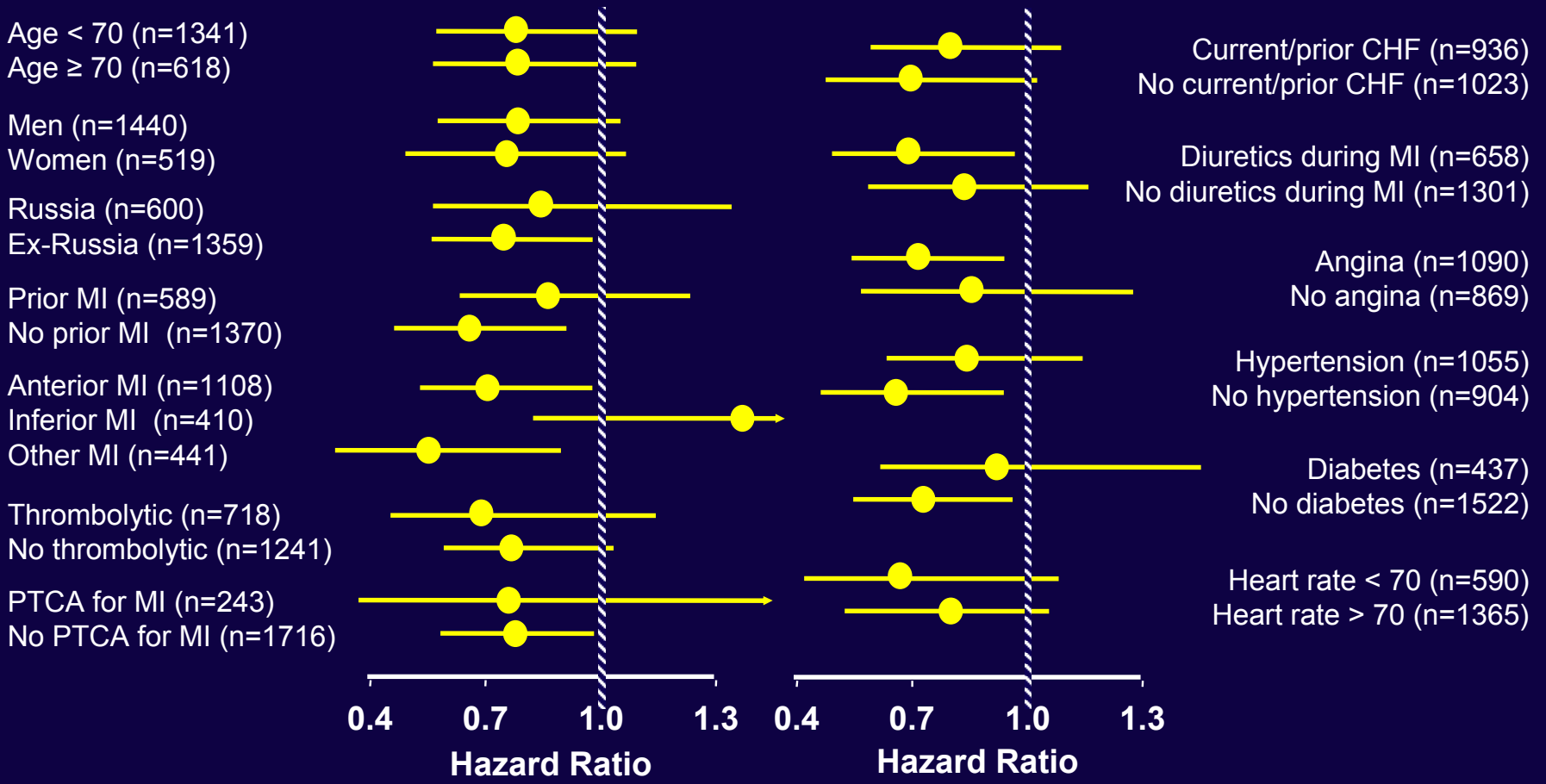
| | Placebo | Carvedilol | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|
| CV death or MI (post-MI β-blocker trials, TRACE) | 181 | 128 | 0.70 (0.56-0.87) | 0.002 |
| CV death, MI or CHF (SAVE) | 258 | 211 | 0.81 (0.68-0.97) | 0.023 |
| Death, MI, CHF or stroke (AIRE) | 276 | 226 | 0.81 (0.68-0.97) | 0.018 |
| Death, MI, CHF or arrhythmia (PRAISE) | 277 | 224 | 0.80 (0.67-0.95) | 0.012 |
| Death, MI, CHF, CVA or arrhythmia (EPHESUS) | 288 | 231 | 0.79 (0.66-0.94) | 0.006 |
| Death, MI/USA, CHF, CVA/TIA, arrhythmia/HB, ↓HR (COPERNICUS) | 327 | 275 | 0.83 (0.70-0.97) | 0.019 |

# *Other Analyses*

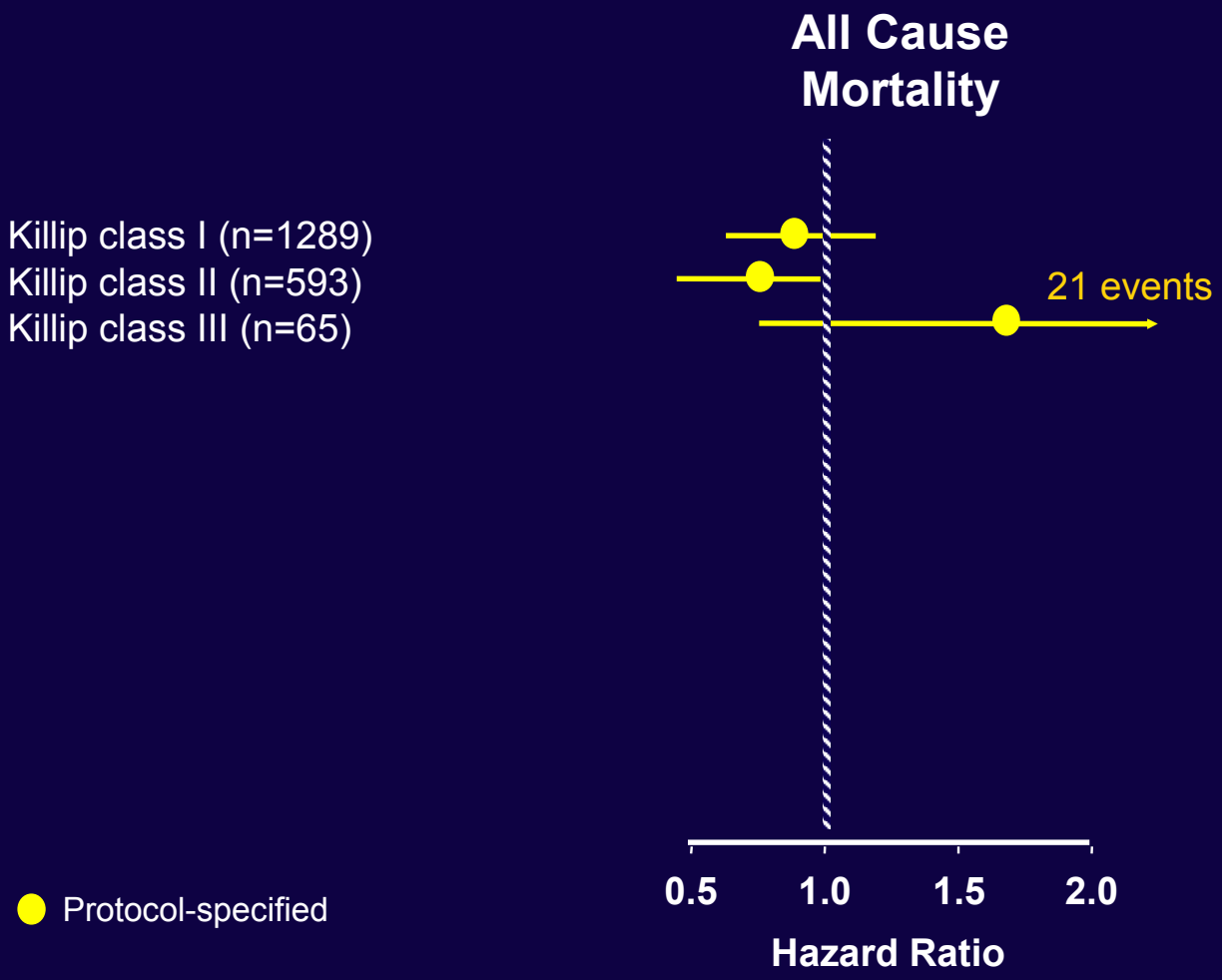
- Mortality subgroups
- Mode of death
- Recurrent myocardial infarction
- Cardiac arrhythmias

# All-Cause Mortality Subgroups

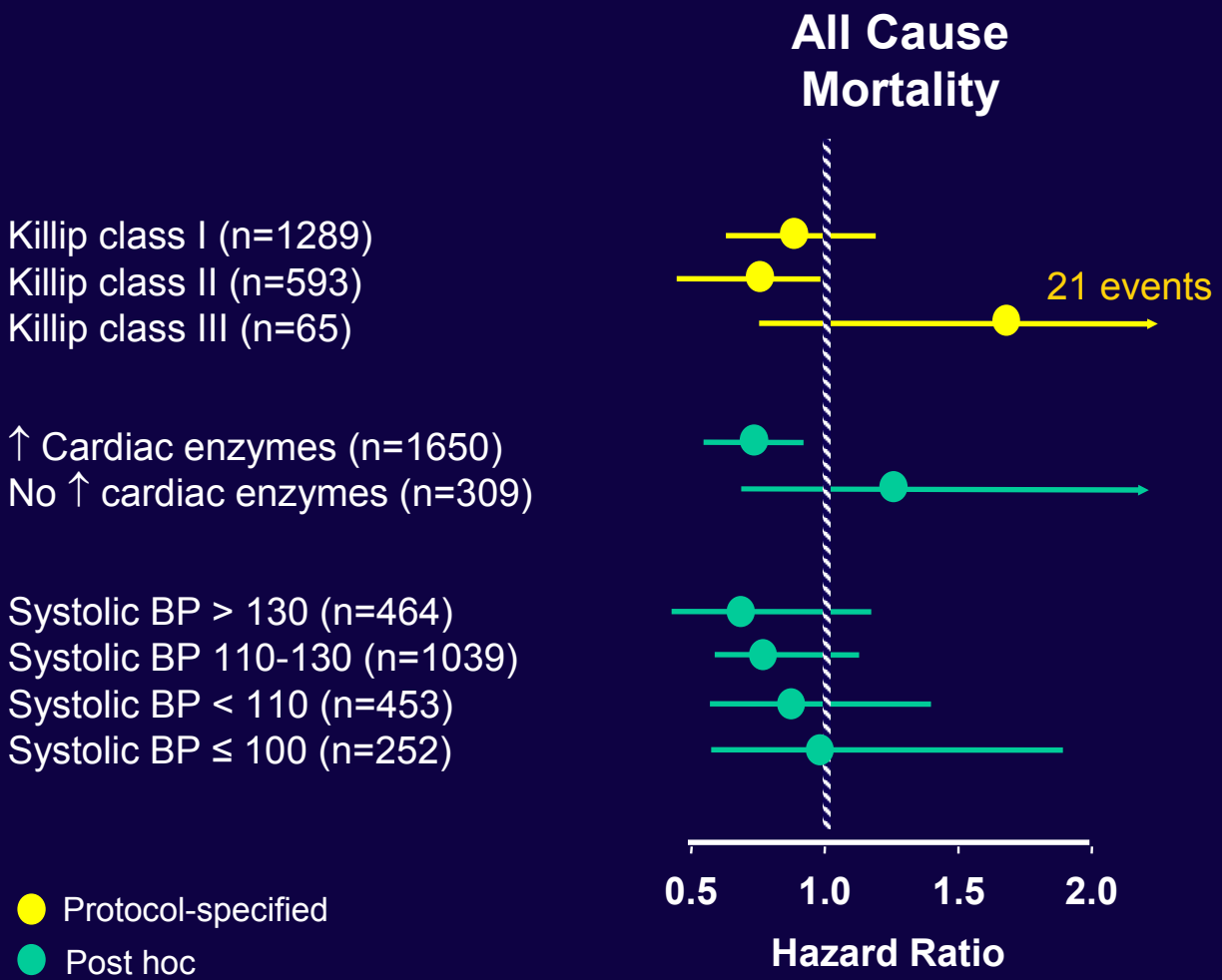
CAPRICORN



# CAPRICORN Subgroups



# CAPRICORN Subgroups



# *Effect of Treatment on Mode of Death in Other Post-MI β-Blocker and Other Carvedilol Trials*

| | **Reported Effect on Mode of Death** |
|---|---|
| Norwegian Timolol Trial | ↓ Cardiovascular death<br>↓ Sudden death |
| Göteborg Metoprolol Trial | No specific information |
| Beta-Blocker Heart Attack Trial | ↓ Cardiovascular death<br>↓ Sudden death |
| COPERNICUS | ↓ Cardiovascular death<br>↓ Sudden death |

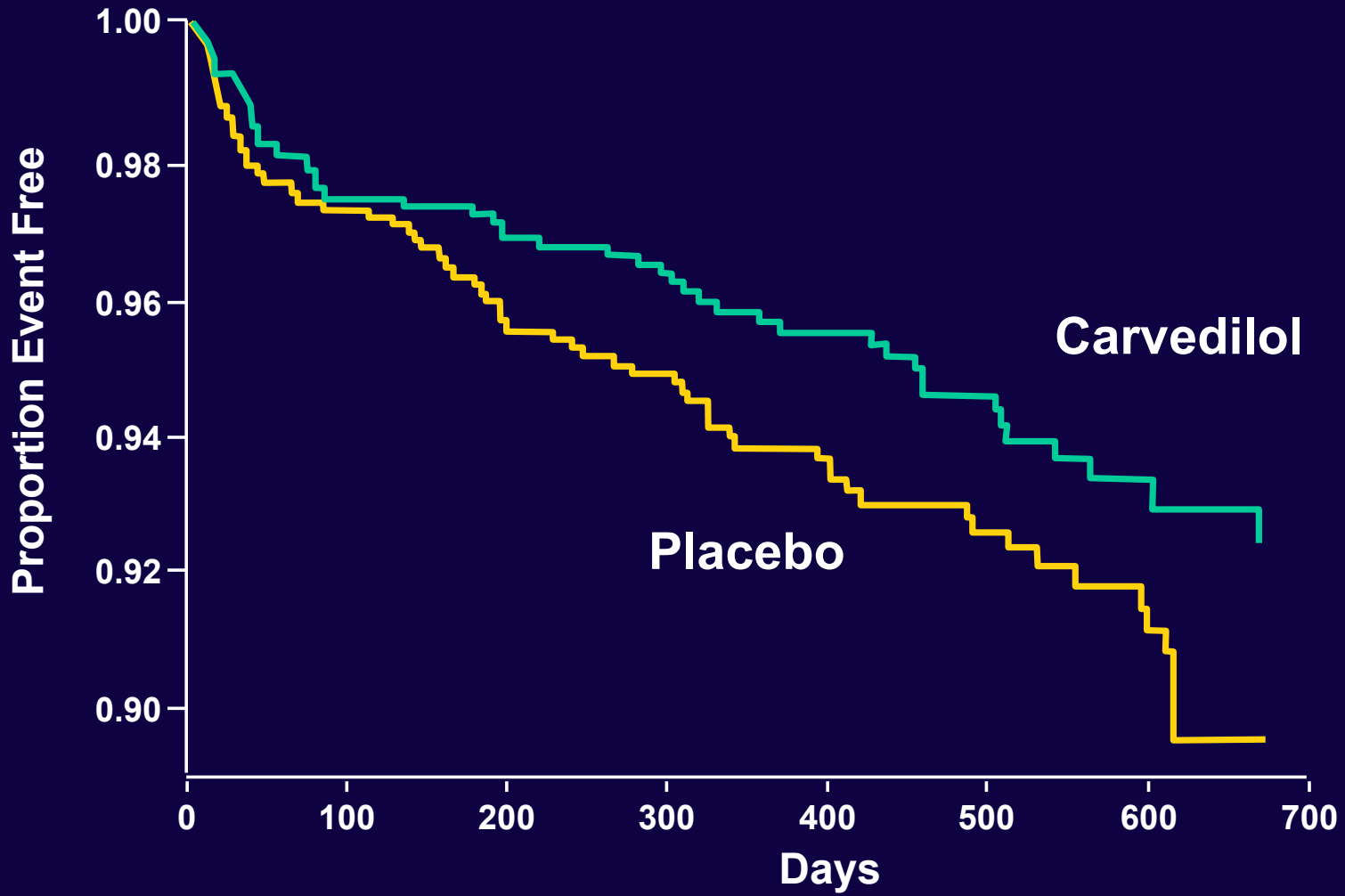
# *Adjudicated Cause of Death*

| | Placebo | Carvedilol | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|
| Cardiovascular death | 139 | 104 | 0.75 (0.58-0.96) | 0.024 |
| Sudden death* | 69 | 51 | 0.74 (0.51-1.06) | 0.099 |
| Death due to worsening heart failure | 30 | 18 | 0.60 (0.33-1.07 | 0.083 |

Asterisk identifies prespecified secondary endpoint.

# Effect on Sudden Death

CAPRICORN



# *Meta-Analysis of Effect of β-Blockers on Non-Fatal MI in Earlier Post-MI Trials*

| | **Earlier Post-MI β-Blocker Trials** |
|---|---|
| Non-fatal recurrent myocardial infarction | 0.74 (0.66, 0.83) |

Based on 1242 events in 18,841 patients enrolled in 24 trials

Yusuf et al., Prog CV Dis 1985; 27:335-371

# *Effect on Recurrent Infarction*

CAPRICORN

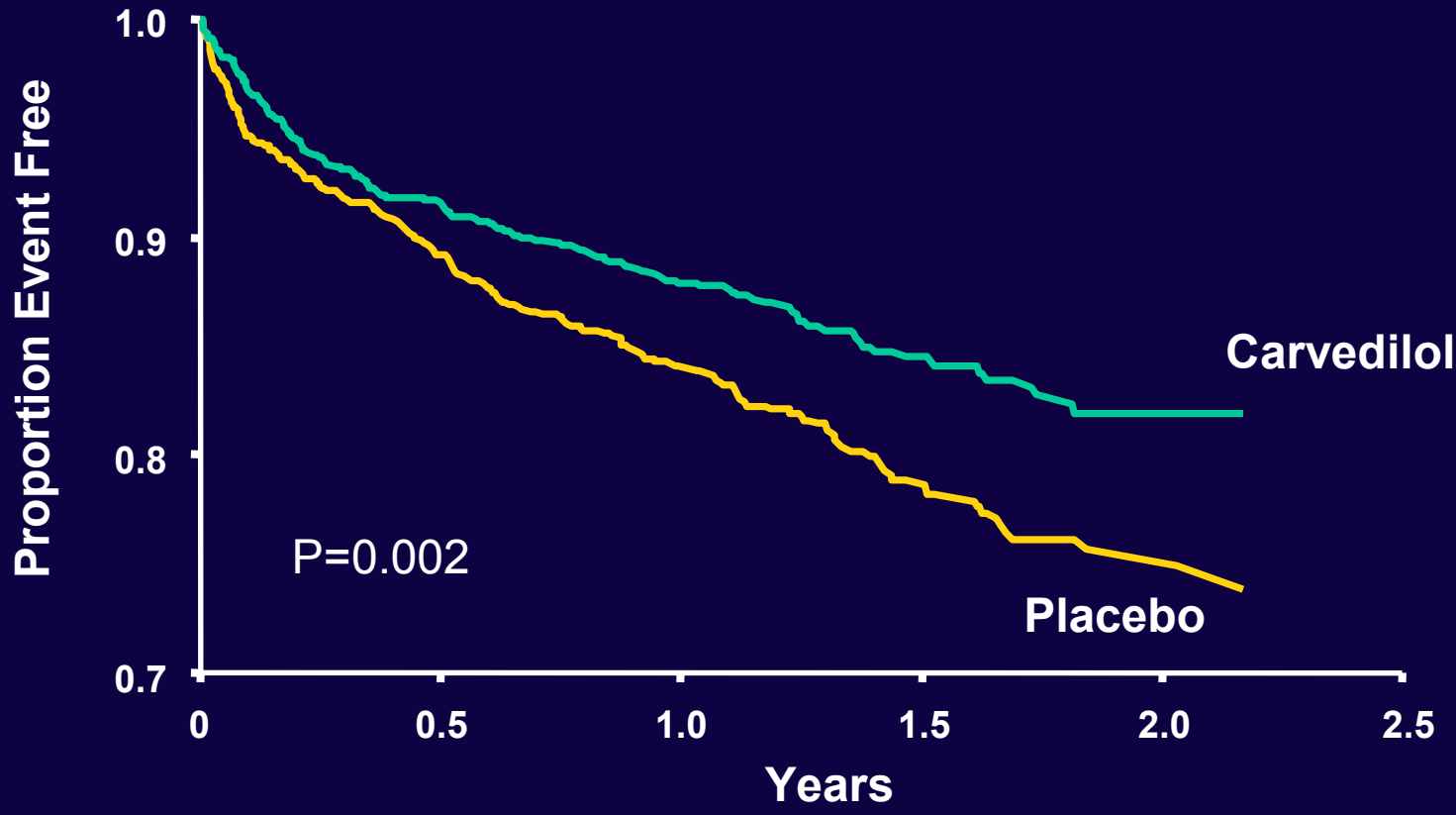
| | Placebo | Carvedilol | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|
| Hospitalization for non-fatal myocardial infarction | 57 | 34 | 0.59 (0.39-0.90) | 0.014 |
| Fatal or non-fatal myocardial infarction | 66 | 40 | 0.60 (0.40-0.89) | 0.010 |
| CV death or non-fatal myocardial infarction | 181 | 128 | 0.70 (0.56-0.87) | 0.002 |
| Any death or non-fatal myocardial infarction | 192 | 139 | 0.71 (0.57-0.89) | 0.002 |

Among first events leading to death or CV hospitalization (co-primary endpoint), 45 of such events on placebo and 27 such events on carvedilol were due to a recurrent infarction.

Total number of hospitalizations for myocardial infarction (including first and recurrent) was 60 in the placebo group and 37 in the carvedilol group.

# All-Cause Mortality or Recurrent Myocardial Infarction

CAPRICORN






*The CAPRICORN Investigators, Lancet 2001*

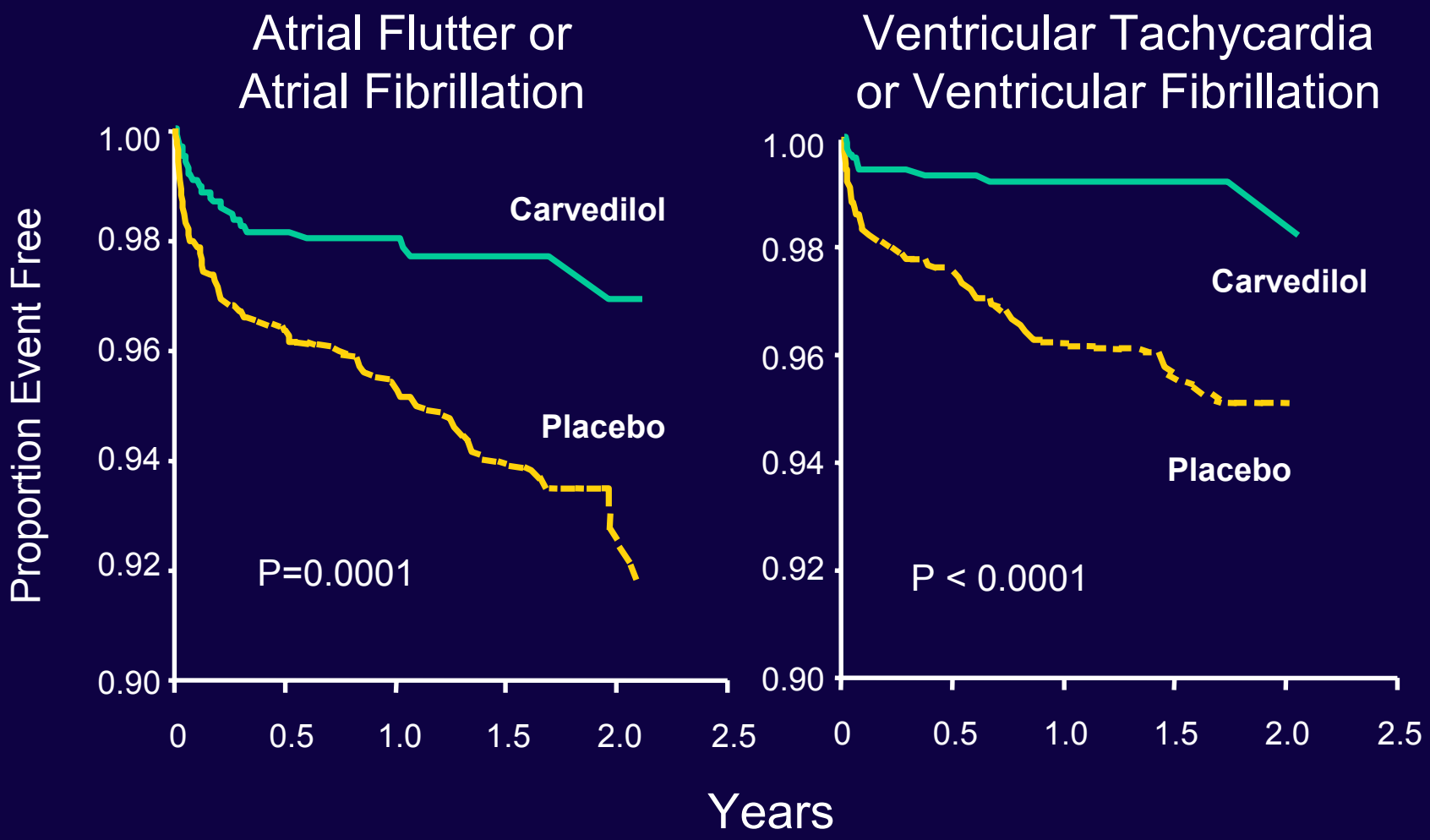
# *Effect of Treatment on Cardiac Arrhythmias in Other Post-MI β-Blocker Trials*

| | **Observed Effect on Arrhythmias** |
|---|---|
| Norwegian Timolol Trial | ↓ Arrhythmias |
| Göteborg Metoprolol Trial | ↓ Arrhythmias |
| Beta-Blocker Heart Attack Trial | ↓ Arrhythmias |
| Lopressor Intervention Trial | ↓ Arrhythmias |

# *Effect on Cardiac Arrhythmia*

| | Placebo | Carvedilol | Hazard ratio (95% CI) | P value |
|---|---|---|---|---|
| Any supraventricular arrhythmia | 54 | 26 | 0.48 (0.30-0.76) | 0.0015 |
| Atrial flutter or atrial fibrillation | 53 | 22 | 0.41 (0.25-0.68) | 0.0003 |
| Any ventricular arrhythmia | 69 | 26 | 0.37 (0.24-0.58) | < 0.0001 |
| Ventricular tachycardia or ventricular fibrillation | 40 | 12 | 0.30 (0.16-0.57) | < 0.0001 |

# Time to First Cardiac Arrhythmia



# *Summary*

- The effect of carvedilol on cardiovascular events was very similar to that seen in other post-infarction β-blocker trials:
  - Reduction in all-cause mortality by 23% (P=0.031) including pattern of subgroup effects
  - Reduction in cardiovascular death by 25% (P=0.024)
  - Reduction in sudden death by 26% (P=0.099)
  - Reduction in non-fatal recurrent MI by 41% (P=0.014)
  - Reduction in fatal and non-fatal MI by 40% (P=0.010)
  - Reduction in CV death and non-fatal MI by 30% (P=0.002)
  - Reduction in atrial fibrillation/flutter by 59% (P=0.0003)
  - Reduction in VT or VF by 70% (P < 0.0001)

# *Summary*

- All of these benefits were observed in patients
  - already taking an ACE inhibitor
  - receiving all appropriate treatments for the immediate and long term management of post-infarction patients.

# *Safety of Carvedilol in the CAPRICORN Trial and Concluding Remarks*

Milton Packer, M.D

# *Concordance of Results of CAPRICORN With Earlier Post-Infarction β-Blocker Trials*

- Concordance of effects on all-cause mortality (including pattern of subgroup effects)
- Concordance of effects on mode of death (e.g., cardiovascular and sudden death)
- Concordance of effects on non-fatal cardio-vascular events (e.g., nonfatal reinfarction and cardiac arrhythmias)
- ?? Concordance of safety profile

# *Safety Issues Identified in Other Post-MI β-Blocker Trials*

| | Reported Adverse Events |
|---|---|
| Norwegian Timolol Trial | ↑ pulmonary edema, ↑ hypotension, ↑ dizziness, ↑ bradycardia, ↑ peripheral vascular symptoms |
| Göteborg Metoprolol Trial | ↑ hypotension, ↑ bradycardia, ↑ heart block |
| Beta-Blocker Heart Attack Trial | ↑ early CHF, ↑ hypotension, ↑ peripheral vascular symptoms |
| Lopressor Intervention Trial | ↑ hypotension, ↑ bradycardia |

# *Adverse Cardiovascular Events More Frequent in Carvedilol Group*

CAPRICORN

| | Placebo (n=980) | Carvedilol (n=969) |
|---|---|---|
| Hypotension | 114 (11.6%) | 176 (18.2%) |
| Dizziness | 105 (10.7%) | 144 (14.9%) |
| Bradycardia | 37 (3.8%) | 63 (6.5%) |
| Lung edema | 31 (3.2%) | 42 (4.3%) |
| Peripheral edema | 28 (2.9%) | 43 (4.4%) |
| Syncope or presyncope | 19 (1.9%) | 38 (3.9%) |
| Peripheral vascular disease | 16 (1.6%) | 30 (3.1%) |
| Postural hypotension | 9 (0.9%) | 20 (2.1%) |

All adverse cardiovascular events with frequency > 2% in either group with ≥ 1% difference between groups

# *Adverse Cardiovascular Events Less Frequent in Carvedilol Group*

CAPRICORN

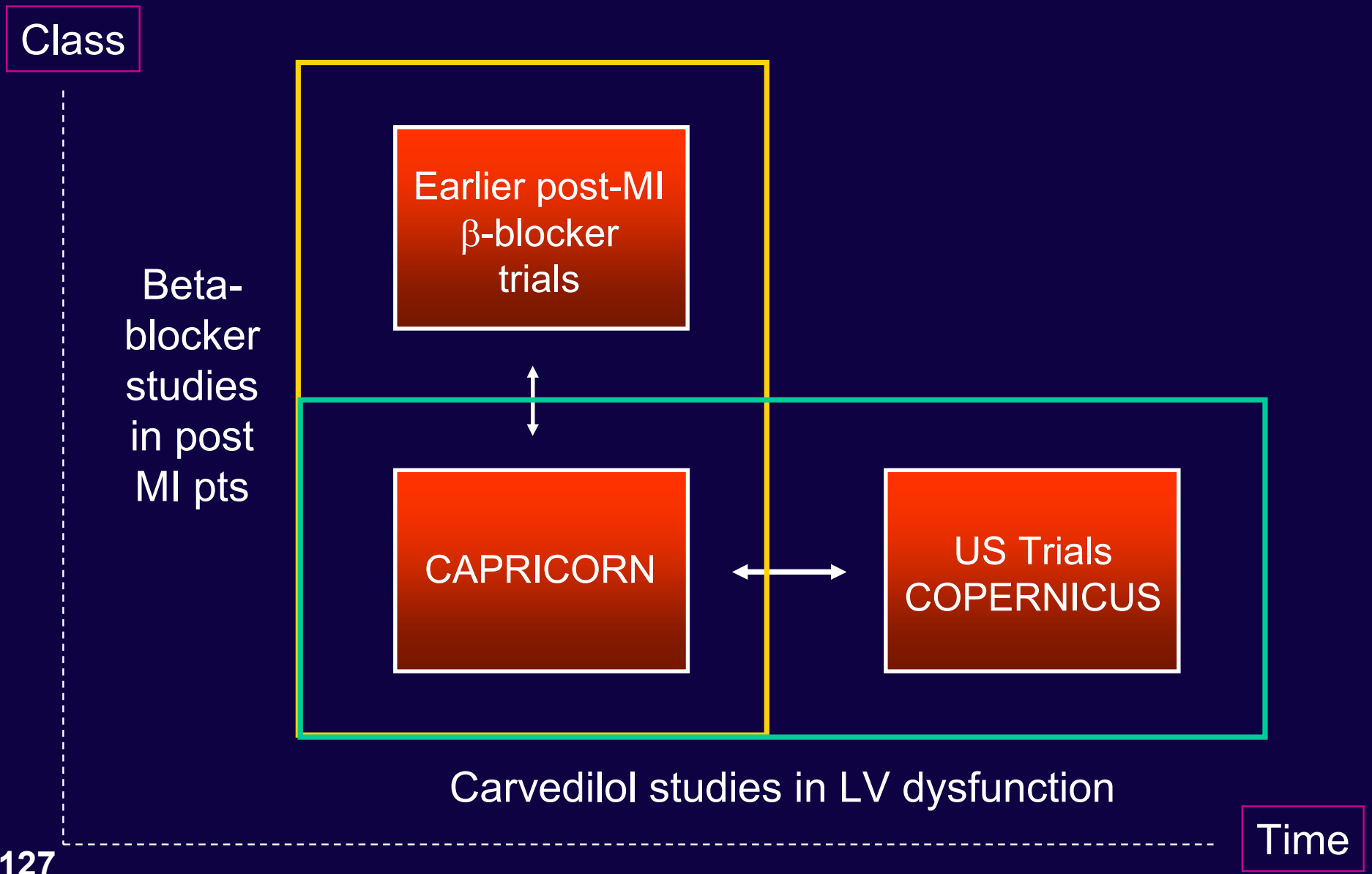
| | Placebo (n=980) | Carvedilol (n=969) |
|---|---|---|
| Angina | 119 (12.1%) | 108 (11.1%) |
| Chest pain | 109 (11.1%) | 97 (10.0%) |
| Myocardial infarction | 89 (9.1%) | 55 (5.7%) |
| Thorax pain | 40 (4.1%) | 28 (2.9%) |
| Atrial fibrillation | 40 (4.1%) | 13 (1.3%) |
| Tachycardia | 27 (2.8%) | 14 (1.4%) |
| Nonspecified CV disorder | 25 (2.6%) | 11 (1.1%) |
| Ventricular tachycardia | 20 (2.0%) | 2 (0.2%) |

All adverse cardiovascular events with frequency > 2% in either group with ≥ 1% difference between groups

# *Reports of Serious Adverse Events*

| | Placebo | Carvedilol |
|---|---|---|
| Heart failure | 91 (9.3%) | 78 (8.0%) |
| Myocardial infarction | 88 (9.0%) | 54 (5.6%) |
| Atrial fibrillation | 16 (1.6%) | 2 (0.2%) |
| Ventricular tachycardia | 15 (1.5%) | 1 (0.1%) |
| Cardiac arrest | 14 (1.4%) | 6 (0.6%) |
| Hypotension | 2 (0.2%) | 13 (1.3%) |

All serious adverse events with frequency > 1% in either group with >1% difference between groups


Class
Beta-blocker studies in post MI pts
Earlier post-MI β-blocker trials
CAPRICORN
US Trials COPERNICUS
Carvedilol studies in LV dysfunction
Time

# *One Last Question*

Even if the Committee were to agree that the mortality finding in the CAPRICORN trial is credible and persuasive, why should it recommend incorporation of the results of the CAPRICORN trial into current labeling for carvedilol?

# *Is There a Need to Recommend the Approval of Carvedilol for the Post-Infarction Setting?*

- No data to recommend the addition of any β-blocker currently approved for use in infarct survivors to an ACE inhibitor (or post-infarction treatments) in patients who have LV dysfunction following their acute infarction.
- All β-blockers currently approved for use in infarct survivors carry a contraindication for use in patients with heart failure.
- The frequency of use of any β-blocker in post-infarction patients with LV dysfunction is low.

# *Is There a Need to Recommend the Approval of Carvedilol for the Post-Infarction Setting?*

- Such use will remain low unless physicians are educated about the earlier administration of β-blockers in patients likely to require them in the future.
- Best opportunity for intervention exists when patients are in the hospital after they have been stabilized following their acute infarction.
- Among approved β-blockers, the most persuasive data in post-infarction patients with LV dysfunction receiving an ACE inhibitor exist for carvedilol.

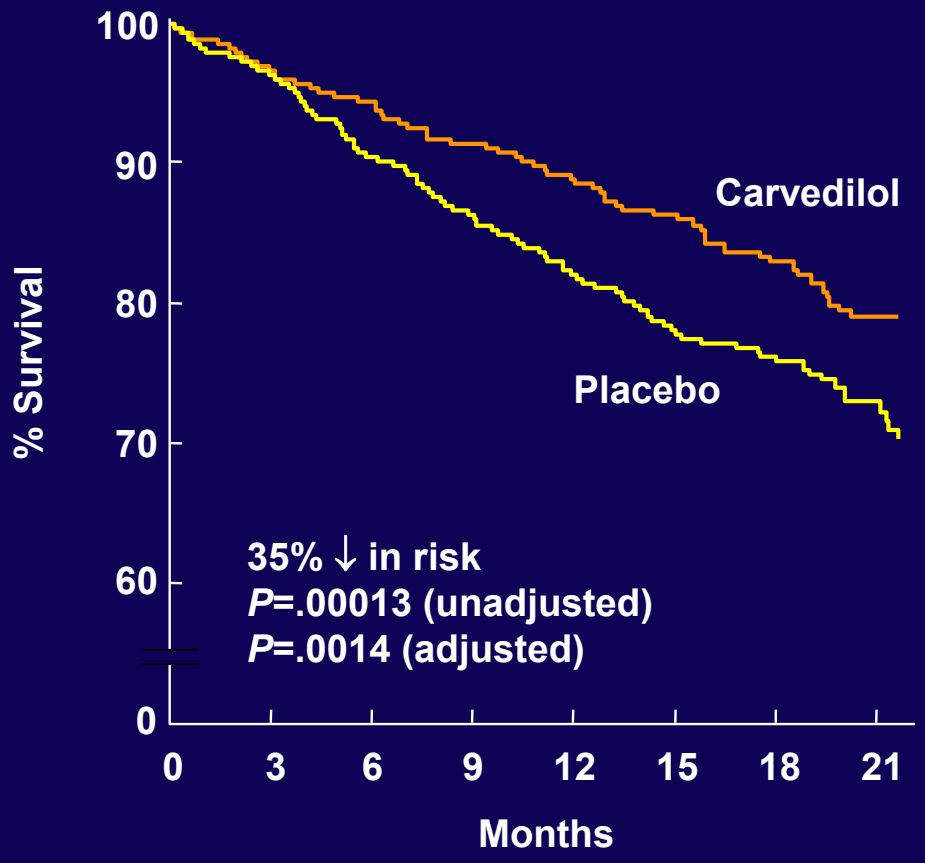
# DSMB Meeting #5 (March 10, 1999)

## Closed Section

- "The best option was thought to be a change of the primary endpoint to Death or cardiovascular hospitalization, keeping the target number of events for the primary endpoint unchanged. This would substantially increase the event rate and would allow the study to be completed in good order. Professor Julian was asked to write to the Steering Committee with this proposal."
- Despite change in primary endpoint, stopping rules were still to be based on all-cause mortality.

# COPERNICUS

## All-Cause Mortality






Packer M., et al. *N Engl J Med.* 2001;344:1651–1658.

# *Why Was Cardiovascular Hospitalization Defined To Include All Such Events?*

- Original protocol paid little attention to definition of CV hospitalization because it was a secondary endpoint. Steering Committee assigned responsibility for defining CV hospitalization to Endpoint Committee.
- Endpoint Committee defined CV hospitalization as hospitalizations for which there was no clear non-CV cause. Committee did not target reasons that might be favorably influenced by β-blockade.
- Steering Committee was reluctant to make too many changes. When it changed the primary endpoint (by simply elevating a secondary endpoint), it was reluctant to change the definition of the endpoint.

# Effect of Carvedilol on Primary Endpoints According to Prior Use of b-Blockers

| | | Death or CV Hospitalization | All-Cause Mortality |
|---|---|---|---|
| Oral or IV β-blocker during/after index MI | Yes (n=728) | 0.93 (0.71, 1.20) [n=226] | 0.77 (0.49, 1.23) [n=74] |
| | No (n=1231) | 0.92 (0.77, 1.10) [n=481] | 0.76 (0.57, 1.01) [n=193] |

Number in brackets under each hazard ratio denotes number of events

# *Reasons for Other CV Hospitalization*

| | Placebo (n=984) | Carvedilol (n=975) |
|---|---|---|
| Atypical chest pain | 2 | 3 |
| Dyspnea or edema | 3 | 2 |
| Peripheral vascular disease | 5 | 2 |
| Venous thrombosis/pulmonary embolism | 3 | 5 |
| Hypotension | 2 | 5 |
| Syncope | 3 | 6 |
| Pericardial disease | 1 | 2 |
| Cardiovascular procedure or its complication | 3 | 3 |
| Miscellaneous events occurring once | 2 | 3 |
| Not classified | 2 | 3 |
| Total | 26 | 34 |

# *Adverse CV Events (Frequency ≥ 1.5%) in Either Treatment Group (Uptitration Phase)*

| | Placebo (n=980) | Carvedilol (n=969) |
|---|---|---|
| Hypotension | 81 (8.3%) | 125 (12.9%) |
| Dizziness | 55 (5.6%) | 96 (9.9%) |
| Heart failure | 42 (4.3%) | 47 (4.9%) |
| Angina pectoris | 41 (4.2%) | 41 (4.2%) |
| Bradycardia | 28 (2.9%) | 45 (4.6%) |
| Chest pain | 34 (3.5%) | 39 (4.0%) |
| Myocardial infarction | 28 (2.9%) | 13 (1.3%) |
| Atrial fibrillation | 19 (1.9%) | 8 (0.8%) |
| Peripheral edema | 14 (1.4%) | 15 (1.5%) |
| Lung edema | 8 (0.8%) | 19 (2.0%) |
| Syncope or presyncope | 4 (0.4%) | 15 (1.5%) |

# Total Number of Hospitalizations for Specified Reasons

| | Placebo (n=984) | Carvedilol (n=975) |
|---|---|---|
| Hospitalizations for any reason | 693 | 621 |
| Hospitalization due to myocardial infarction | 60 | 37 |
| Hospitalization due to worsening heart failure | 181 | 151 |
| Hospitalization due to unstable angina | 53 | 56 |
| Hospitalization due to stroke or TIA | 18 | 17 |
| Hospitalization due to other angina or chest pain | 84 | 92 |
| Hospitalizations for presumed or other CV reason | 70 | 79 |
| Hospitalization for cardiovascular procedure | 93 | 84 |
| Hospitalization for non-cardiovascular reasons | 123 | 96 |
| Failed to meet criteria for inclusion as hospitalization | 11 | 9 |

Hospitalizations with more than one cause were counted only once and attributed to the worst event listed as a reason for the admission (myocardial infarction > heart failure > unstable angina > stroke > TIA > other angina or chest pain > nonclassified or other > cardiovascular procedure > noncardiovascular).

# *Effect of Study Drug on Duration of Index Hospitalization*

| | Placebo | Carvedilol |
|---|---|---|
| Duration of index hospitalization (days) | 17.9 | 17.3 |
| Number of patients who had event that prolonged index hospitalization | 145 | 91 |